PB91-181537

Toxicological Profile for Polycyclic Aromatic Hydrocarbons

Clement Associates, Inc., Fairfax, VA

Prepared for:

Agency for Toxic Substances and Disease Registry, Atlanta, GA

Dec 90

U.S. Department of Commerce
National Technical Information Service
NTIS

PB91-181537

TOXICOLOGICAL PROFILE FOR POLYCYCLIC AROMATIC HYDROCARBONS

Prepared by:

Clement International Corporation
Under Contract No. 205-88-0608

Prepared for:

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

December 1990

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA 22161

50272-101

REPORT DOCUMENTATION PAGE	**1. REPORT NO.** ATSDR/TP -90-20	**2.**	**3** PB91-181537

4. Title and Subtitle
Toxicological Profile for POLYCYCLIC AROMATIC HYDROCARBONS

5. Report Date

6.

7. Author(s)
ATSDR

8. Performing Organization Rept. No.
ATSDR/TP -90-20

9. Performing Organization Name and Address
Agency for Toxic Substances and Disease Registry (ATSDR)
1600 Clifton Road, N.E.
Atlanta, Georgia 30333
in collaboration with
U.S. Environmental Protection Agency (EPA)

10. Project/Task/Work Unit No.

11. Contract(C) or Grant(G) No.
(C) 205-88-0608
(G)

12. Sponsoring Organization Name and Address
Agency for Toxic Substances and Disease Registry (ATSDR)
1600 Clifton Road, N.E.
Atlanta, Georgia 30333

13. Type of Report & Period Covered
Final

14.

15. Supplementary Notes
This report was prepared as required by section 110 (3) of the Superfund Amendments and Reauthorization Act of 1986 (42 U.S.C. 9618(f)

16. Abstract (Limit: 200 words)

The ATSDR Toxicological Profile for Polycyclic Aromatic Hydrocarbons (PAHs): Acenaphthene, Acenaphthylene, Anthracene, Benzo(a)anthracene, Benzo(a)pyrene, Benzo(b)fluoranthene, Benzo(g,h,i)perylene, Benzo(k)fluoranthene, Chrysene, Dibenzo(a,h)anthracene, Fluoranthene, Fluorene, Indeno(1,2,3-cd)pyrene, Phenanthrene, Pyrene is intended to characterize succinctly the toxicological and health effects information for the substance. It identifies and reviews the key literature that describes the substance's toxicological properties. Other literature is presented but described in less detail. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced. The profile begins with a public health statement, which describes in nontechnical language the substance's relevant toxicological properties. Following the statement is material that presents levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine the substance's health effects is described. Research gaps in nontoxic and health effects information are described. Research gaps that are of significance to the protection of public health will be identified in a separate effort. The focus of the document is on health and toxicological information.

17. Document Analysis a. Descriptors
POLYCYCLIC AROMATIC HYDROCARBONS
Environment
Human health effects
Toxicity

b. Identifiers/Open-Ended Terms
Levels of significant human exposure
Profiles
Superfund

c. COSATI Field/Group

18. Availability Statement
No restrictions on distribution
Available from NTIS, Springfield, VA 22161

19. Security Class (This Report)
UNCLASSIFIED

20. Security Class (This Page)
UNCLASSIFIED

21. No. of Pages

22. Price

(See ANSI-Z39.18) *See Instructions on Reverse* OPTIONAL FORM 272 (4-77)
(Formerly NTIS-35)
Department of Commerce

Toxicological Profile for

PB91-181537

POLYCYCLIC AROMATIC HYDROCARBONS

ACENAPHTHENE
ACENAPHTHYLENE
ANTHRACENE
BENZO(a)ANTHRACENE
BENZO(a)PYRENE
BENZO(b)FLUORANTHENE
BENZO(g,h,i)PERYLENE
BENZO(k)FLUORANTHENE
CHRYSENE
DIBENZO(a,h)ANTHRACENE
FLUORANTHENE
FLUORENE
INDENO(1,2,3-cd)PYRENE
PHENANTHRENE
PYRENE

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

TP-90-20

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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987, on October 20, 1988, on October 26, 1989, and on October 17, 1990.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects,

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects, and

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by CERCLA, as amended.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning significant health effects associated with exposure to the substance. The adequacy of information to determine a substance's health effects is described. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

William L. Roper

William L. Roper, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about polycyclic aromatic hydrocarbons (PAHs) and to emphasize the human health effects that may result from exposure to them. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). At this time, all of the polycyclic aromatic hydrocarbons discussed in this profile have been found at several of these NPL hazardous waste sites. Dibenz(a,h)anthracene has been found at the lowest number of sites (6) and benzo(a)pyrene has been found at the highest number of sites (84). However, we do not know how many of the 1,177 NPL sites have been evaluated for PAHs. As EPA evaluates more sites, the number of sites at which PAHs are found may change. The information is important for you because PAHs may cause harmful health effects and because these sites are potential or actual sources of human exposure to PAHs.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to hazardous substances such as PAHs, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT ARE POLYCYCLIC AROMATIC HYDROCARBONS?

PAHs are a group of chemicals that are formed during the incomplete burning of coal, oil and gas, garbage, or other organic substances. PAHs can be man-made or occur naturally. There is no known use for most of these chemicals except for research purposes. A few of the PAHs are used in medicines and to make dyes, plastics, and pesticides. They are found throughout the environment in the air, water, and soil. There are over one hundred different PAH compounds. Although the health effects of the individual PAHs are not exactly alike, the following 15 PAHs are considered as a group in this profile:

- acenaphthene
- acenaphthylene
- anthracene

- benz(a)anthracene
- benzo(a)pyrene
- benzo(b)fluoranthene
- benzo(ghi)perylene
- benzo(k)fluoranthene
- chrysene
- dibenz(a,h)anthracene
- fluoranthene
- fluorene
- indeno(1,2,3-cd)pyrene
- phenanthrene
- pyrene

As pure chemicals, PAHs generally exist as colorless, white, or pale yellow-green solids. Most PAHs do not occur alone in the environment (including those found at hazardous waste sites), rather they are found as mixtures of two or more PAHs. They can occur in the air either attached to dust particles, or in soil or sediment as solids. They can also be found in substances such as crude oil, coal, coal tar pitch, creosote, and road and roofing tar. Most PAHs do not dissolve easily in water, but some PAHs readily evaporate into the air. PAHs generally do not burn easily and they will last in the environment for months to years.

More information on the chemical and physical properties of PAHs can be found in Chapter 3 and on their occurrence and break down in the environment in Chapter 5.

1.2 HOW MIGHT I BE EXPOSED TO POLYCYCLIC AROMATIC HYDROCARBONS?

PAHs are present throughout the environment, and you may be exposed to these substances at home, while outside, or at the workplace. Typically, you will not be exposed to an individual PAH alone, but to a mixture of PAHs.

In the environment, you are exposed to PAH vapors or PAHs that are attached to dust and other particles in the air. Other sources include vehicle exhausts, asphalt roads, coal, coal tar, wild fires, agricultural burning, and hazardous waste sites. Background levels of PAHs in the air are reported to be 0.02-1.2 mg/m^3 in rural areas and 0.15-19.3 mg/m^3 in urban areas. You may be exposed to PAHs in soil near areas where coal, wood, gasoline, or other products have been burned. You may be exposed to PAHs in the soil on or near hazardous waste sites, such as former manufactured-gas sites and wood-preserving facilities. PAHs have been found in some drinking water supplies in the United States. The background level of PAHs in drinking water ranges from 4 to 24 nanograms per liter (ng/L).

In the home, PAHs are present in tobacco smoke, smoke from home heating of wood, creosote-treated wood products, cereals, grains, flour, bread, vegetables, fruits, meat, processed or pickled foods, and beverages. Food grown in contaminated soil or air may also contain PAHs. Cooking meat or other food at high temperatures, which happens during grilling or charring, increases the amount of PAHs in the food. The level of PAHs in the typical U.S. diet is less than 2 parts of total PAHs per billion parts of food (ppb).

For many people, the greatest exposure to PAHs occurs in the workplace. PAHs have been found in coal-tar production plants, coking plants, bitumen and asphalt production plants, coal-gasification sites, smoke houses, aluminum production plants, coal-tarring activities, and municipal trash incinerators. PAHs have also been found in other facilities where petroleum, petroleum products, or coal are used or where wood, cellulose, corn, or oil are burned. For more information on human exposure to PAHs see Chapter 5.

1.3 HOW CAN POLYCYCLIC AROMATIC HYDROCARBONS ENTER AND LEAVE MY BODY?

PAHs can enter your body through your lungs when you breathe air that contains them. This is one of the most significant route of exposure for people living near hazardous waste sites. Drinking water or swallowing food, soil, or dust particles that contain PAHs are other routes for these chemicals to enter your body. Under normal conditions of environmental exposure, PAHs could enter your body if your skin comes into contact with soil that contains high levels of PAHs (this could occur near a hazardous waste site); or with heavy oils or other products (such as coal tar, roofing tar, or creosote) that contain PAHs.

PAHs enter your body quickly and easily by all routes of exposure. The rate at which PAHs enter your body is increased when they are present in oily mixtures. They go to all the tissues of your body that contain fat, and tend to be stored mostly in your kidneys, liver, and fat, with smaller amounts in your spleen, adrenal glands, and ovaries. Results from animal studies show that PAHs do not tend to be stored in your body for a long time; most PAHs that enter the body leave within a few days, primarily in the feces and urine. More information on how PAHs enter and leave your body can be found in Chapters 2 and 6.

1.4 HOW CAN POLYCYCLIC AROMATIC HYDROCARBONS AFFECT MY HEALTH?

PAHs can cause harm to your health. Several of the PAHs, including benz(a)anthracene, benzo(a)pyrene, benzo(b)fluoranthene, benzo(k)fluoranthene, chrysene, dibenz(a,h)anthracene, indeno(1,2,3-cd)pyrene, have caused tumors in laboratory animals when they ate them, when they were applied to their skin, or when they breathed them in the air for long periods of time. Reports in humans show that individuals exposed by breathing or skin contact for long periods of time to mixtures of other compounds and PAHs can also develop cancer.

Mice fed high levels of benzo(a)pyrene during pregnancy had difficulty reproducing and so did their offspring. The offspring from pregnant mice fed benzo(a)pyrene also showed other harmful effects, such as birth defects and decreased body weight. Similar effects could occur in humans, but we have no information to show that these effects do occur.

Studies in animals have also shown that PAHs can cause harmful effects on skin, body fluids, and the body's system for fighting disease after both short- and long-term exposure. These effects have not been reported in humans. More information on the health effects associated with exposure to PAHs can be found in Chapter 2.

1.5 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

Tables 1-1 through 1-4 show the relationship between exposure to PAHs and known health effects in humans and animals. As can be seen, no information is available from human studies to determine health effects resulting from exposure to specific levels of the individual PAHs, although inhalation and skin exposure to mixtures containing PAHs has been associated with cancer in humans.

A Minimal Risk Level (MRL) is also included in Table 1-3. This MRL was derived from animal data for short-term exposure, as described in Chapter 2 and in Table 2-2. The MRL provides a basis for comparison with levels that people might encounter in food. If a person is exposed to PAHs at an amount below the MRL, it is not expected that harmful (noncancer) health effects will occur. Because this level is based only on information currently available, some uncertainty is always associated with it. Also, because the method for deriving MRLs does not use any information about cancer, an MRL does not imply anything about the presence, absence, or level of risk for cancer.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO POLYCYCLIC AROMATIC HYDROCARBONS?

In your body, PAHs are changed into chemicals that can attach to substances within the body. The presence of PAHs attached to these substances can then be measured in body tissues or blood after exposure to PAHs. However, this test is still being developed and it is not known yet how well it works. PAHs or their breakdown products can also be measured in urine. Although these tests can tell that you have been exposed to PAHs, it is not yet possible to use these tests to predict the severity of any health effects that might occur or to determine the extent of your exposure to the PAHs. These tests are not routinely available at a doctor's office because they require special equipment for sampling and detecting these chemicals. More information on tests used to determine PAHs in your body is presented in Chapters 2 and 6.

TABLE 1-1. Human Health Effects from Breathing PAHs*

Short-term Exposure (less than or equal to 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from short-term exposure of humans to air containing specific levels of PAHs are not known.
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from long-term exposure of humans to air containing specific levels of PAHs are not known.

*See Section 1.2 for a discussion of exposures encountered in daily life.

TABLE 1-2. Animal Health Effects from Breathing PAHs

Short-term Exposure (less than or equal to 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from short-term exposure of animals to air containing specific levels of PAHs are not known.
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects*
		The health effects resulting from long-term exposure of animals to air containing specific levels of PAHs are not known.

TABLE 1-3. Human Health Effects from Eating or Drinking PAHs*

<table>
<tr><th colspan="3">Short-term Exposure
(less than or equal to 14 days)</th></tr>
<tr><th>Levels in Food (ppm)</th><th>Length of Exposure</th><th>Description of Effects</th></tr>
<tr><td>3.6</td><td></td><td>Minimal Risk Level (based on animal studies; see Section 1.5 for discussion).</td></tr>
<tr><th>Levels in Water (ppm)</th><th></th><th></th></tr>
<tr><td></td><td></td><td>The health effects resulting from short-term exposure of humans to water containing specific levels of PAHs are not known.</td></tr>
<tr><th colspan="3">Long-term Exposure
(greater than 14 days)</th></tr>
<tr><th>Levels in Food (ppm)</th><th>Length of Exposure</th><th>Description of Effects</th></tr>
<tr><td></td><td></td><td>The health effects resulting from long-term exposure of humans to food containing specific levels of PAHs are not known.</td></tr>
<tr><th>Levels in Water (ppm)</th><th></th><th></th></tr>
<tr><td></td><td></td><td>The health effects resulting from long-term exposure of humans to water containing specific levels of PAHs are not known.</td></tr>
</table>

*See Section 1.2 for a discussion of exposures encountered in daily life.

TABLE 1-4. **Animal Health Effects from Eating or Drinking PAHs**

Short-term Exposure (less than or equal to 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects*
308	10 days	Birth defects caused by benzo(a)pyrene in mice.
Levels in Water (ppm)		
		The health effects resulting from short-term exposure of animals to water containing specific levels of PAHs are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects*
923	6 months	Adverse effects on the liver and blood in mice caused by benzo(a)pyrene.
Levels in Water (ppm)		
		The health effects resulting from long-term exposure of animals to water containing specific levels of PAHs are not known.

*These effects are listed at the level at which they were first observed. They may also be seen at higher levels.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

Based on data on benzo(a)pyrene, the federal government has developed regulatory standards and guidelines to protect individuals from the potential health effects of PAHs in drinking water. The U.S. Environmental Protection Agency (EPA) has provided estimates of levels of total cancer-causing PAHs in lakes and streams associated with various risks of developing cancer in humans. EPA has also concluded that any release of PAHs of more than 1 pound should be reported.

PAHs are generally not produced commercially in the United States except as research chemicals. However, PAHs are found in coal, coal tar, and in the creosote oils and pitches formed from the distillation of coal tars. The National Institute for Occupational Safety and Health (NIOSH) concluded that occupational exposure to coal products can increase the risk of lung and skin cancer in workers and recommended an occupational exposure limit for coal tar products of 0.1 milligram of PAHs per cubic meter of air (0.1 mg/m^3) for a 10-hour workday, 40-hour work week. The Occupational Safety and Health Administration (OSHA) has established a legally enforceable limit of 0.2 milligrams of all PAHs per cubic meter of air (0.2 mg/m^3).

More information on regulations and advisories for PAHs exposure can be found in Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your State Health or Environmental Department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

This agency can also give you information on the location of the nearest occupational and environmental health clinics. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to polycyclic aromatic hydrocarbons. Its purpose is to present levels of significant exposure for polycyclic aromatic hydrocarbons based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of polycyclic aromatic hydrocarbons and (2) a depiction of significant exposure levels associated with various adverse health effects.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the data in this section are organized first by route of exposure -- inhalation, oral, and dermal -- and then by health effect -- death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods -- acute, intermediate, and chronic.

Levels of significant exposure for each exposure route and duration (for which data exist) are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown on the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) are of interest to health professionals and citizens alike.

For certain chemicals, levels of exposure associated with carcinogenic effects may be indicated in the figures. These levels reflect the actual doses associated with the tumor incidences reported in the studies cited. Because cancer effects could occur at lower exposure levels, the figures also show estimated excess risks, ranging from a risk of one in 10,000 to one in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1989a), uncertainties are associated with the techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of these procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Fifteen PAHs have been combined in this one profile. These 15 PAHs were selected using the following three criteria:

1) Toxicity
2) Potential for human exposure
3) Frequency of occurrence at NPL hazardous waste sites

The 15 PAHs were combined into one profile to avoid repetition across multiple profiles on the individual PAHs since these chemicals often occur together in the environment and many have similar toxicological effects, environmental fate, etc. Those instances where it is known that the various PAHs differ with regard to toxicological effects or environmental fate will be pointed out. For example, PAHs can be classified as "alternant" (e.g. benzo(a)pyrene, benz(a)anthracene, chrysene, dibenz(a,h)anthracene) or "non-alternant" (e.g. fluoranthene, benzo(k)fluoranthene, benzo(j)fluoranthene, indeno(1,2,3-cd)pyrene). This distinction is based on the electron density associated with the molecule. Alternant PAHs have an equally distributed electron density whereas non-alternant PAHs behave almost as if they were two different molecules because of an uneven distribution of electron density from one portion of the molecule to another. The toxicological significance of this difference is that alternant and non-alternant PAHs appear to behave differently, for example, with regard to how they are metabolized to ultimate carcinogens (see Section 2.3.3, Metabolism).

Reliable health-based and environmental information exists on only a few of the 15 PAHs discussed in this profile, and the potential health effects of the other less well-studied PAHs must be inferred from this information. By combining all 15 PAHs in one profile, these comparisons and inferences can easily be made. Although a large toxicity database exists on complex mixtures that contain PAHs (such as crude oils, various high boiling point distillates, complex petroleum products, coal tars, creosote, and the products of coal liquification processes), these data generally have not been used in this profile. It is difficult to ascertain the toxicity of the component PAHs in these mixtures because of the potential interactions that could occur and the presence of other toxic substances in the mixtures. Furthermore, ATSDR has developed a profile on one of these complex mixtures, creosote, and the reader is referred to this profile for information on this complex mixture (ATSDR 1990). However, most of the available information on the health effects of PAHs in humans must be inferred from studies that reported the effects of exposure to complex mixtures that contain PAHs. Epidemiologic studies have shown increased mortality due to lung cancer in humans exposed to coke-oven emissions, roofing-tar emissions, and cigarette smoke. Each of these mixtures contains benzo(a)pyrene, chrysene, benz(a)anthracene, benzo(b)fluoranthene, and dibenz(a,h)anthracene as well as other potentially carcinogenic PAHs and other carcinogenic and potentially carcinogenic chemicals, tumor promoters, initiators, and cocarcinogens such as nitrosamines, coal tar pitch, and creosote. It is thus impossible to evaluate the contribution of any individual PAH to the total carcinogenicity of these mixtures in humans because of the complexity of the mixtures and the presence of other carcinogens. Despite these limitations, reports of this nature provide qualitative evidence of the potential for mixtures containing PAHs such as benzo(a)pyrene, chrysene, benz(a)anthracene, benzo(b)fluoranthene, and dibenz(a,h)anthracene to cause cancer in humans, and for this reason, and the lack of data on the effects of individual PAHs in humans, such information has been included in this profile on PAHs.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding death in humans following inhalation exposure to any of the 15 PAHs discussed in this profile. However, a dose-related decrease in survival was noted in hamsters exposed by inhalation to benzo(a)pyrene for 109 weeks (Thyssen et al. 1981). The authors attributed this reduced survival in part to toxic and carcinogenic effects induced by this PAH (e.g. tumors in the pharynx and larynx that could have inhibited food intake).

No studies were located regarding the following health effects in humans or animals following inhalation exposure to any of the 15 PAHs discussed in this profile.

2.2.1.2 Systemic Effects

2.2.1.3 Immunological Effects

2.2.1.4 Neurological Effects

2.2.1.5 Developmental Effects

2.2.1.6 Reproductive Effects

2.2.1.7 Genotoxic Effects

2.2.1.8 Cancer

No studies were located regarding cancer in humans following inhalation exposure to any of the 15 PAHs discussed in this profile. However, epidemiologic studies have shown increased mortality due to lung cancer in humans exposed to coke-oven emissions (Lloyd 1971; Mazumdar et al. 1975; Redmond et al. 1976), roofing-tar emissions (Hammond et al. 1976), and cigarette smoke (Maclure and MacMahon 1980; Wynder and Hoffmann 1967). Each of these mixtures contains benzo(a)pyrene, chrysene, benz(a)anthracene, benzo(b)fluoranthene, and dibenz(a,h)anthracene as well as other potentially carcinogenic PAHs and other carcinogenic and potentially carcinogenic chemicals, tumor promoters, initiators, and cocarcinogens such as nitrosamines, coal tar pitch, and creosote. It is thus impossible to evaluate the contribution of any individual PAH to the total carcinogenicity of these mixtures in humans because of the complexity of the mixtures and the presence of other carcinogens. Furthermore, the levels of PAHs were not quantitated in any of these reports. It has been reported, however, that the 8 hour time-weighted-average (TWA) exposure to PAHs in older coke plants was approximately 22-33 $\mu g/m^3$ (Blome 1981). Despite these limitations, reports of this nature provide qualitative evidence of the potential for mixtures containing PAHs such as benzo(a)pyrene, chrysene, benz(a)anthracene, benzo(b)fluoranthene, and dibenz(a,h)anthracene to cause cancer in humans.

Several inhalation studies for animals given benzo(a)pyrene were located. The results of one study indicate that inhalation of benzo(a)pyrene alone does not produce a carcinogenic effect (Laskin et al. 1970). However, the chronic study of Thyssen et al. (1981) provides clear-cut evidence of a dose-response relationship between inhaled benzo(a)pyrene particles (99% of the benzo(a)pyrene particles were between 0.2 and 0.54 microns in diameter) and respiratory tract tumorigenesis. Respiratory tract tumors were induced in the nasal cavity, pharynx, larynx, and trachea in a dose-related manner in hamsters exposed to 9.5 mg/m^3 and 46.5 mg/m^3 for 109 weeks. The reason for the absence of lung tumors is not known, since there is some evidence that hamster lung tissue can activate benzo(a)pyrene to carcinogenic intermediates as well as the other respiratory tract tissues (Dahl et al. 1985). Tumors were also observed following exposure to 46.5 mg/m^3 in the esophagus, and forestomach (presumably as a consequence of mucociliary particle clearance)

(Thyssen et al. 1981). These tumor types consisted of papillomas, papillary polyps, and squamous cell carcinomas. The cancer effect level (CEL) from this study is presented in Table 2-1 and plotted in Figure 2-1.

Wistar rats chronically exposed to combustion gases of a coal-burning furnace enriched with a mean concentration of 0.049 mg/m^3 benzo(a)pyrene for 22 months developed lung tumors, 11% of which were identified as squamous cell carcinomas. The mass median aerodynamic diameter of the coal furnace exhaust gas was approximately 0.1 μm, and that of the mixed emissions from the coal furnace and pyrolized pitch was approximately 0.8 μm. At 22 months, 50% of the control and treated animals were dead. At the time the report was published, only 50% of the animals were examined histologically. No tumors were observed in the control animals. However, only one dose was studied, and concomitant exposure to other compounds including hydrocarbons, sulfur, carbon and nitrogen oxides, and methane as well as other PAHs (e.g. fluoranthenes, pyrene, benz(a)anthracene, chrysene, benzofluoranthenes, indeno(1,2,3-cd)pyrene and benzo(ghi)perylene) in the exhaust gas prevents a direct association between benzo(a)pyrene exposure and tumor development in this study (Heinrich et al. 1986).

Respiratory tract tumors have also been observed in rats that inhaled a combination of benzo(a)pyrene and the atmospheric irritant, sulfur dioxide (SO_2). Sulfur dioxide by itself was not carcinogenic (Laskin et al. 1970). Rats exposed to 10 mg/m^3 benzo(a)pyrene in the presence of SO_2 1 hour/day for 1 year exhibited increased incidences of squamous cell carcinomas in the lungs compared to rats exposed to 10 mg/m^3 benzo(a)pyrene alone (Laskin et al. 1970). These results indicate that benzo(a)pyrene is carcinogenic in animals following inhalation exposure. This carcinogenicity can be enhanced with concurrent exposure to gases and particulates commonly found in the environment.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans following oral exposure to any of the 15 PAHs discussed in this profile.

Aryl hydrocarbon hydroxylase is a microsomal enzyme believed to be responsible for the metabolism of benzo(a)pyrene. Oral exposure to 120 mg/kg/day benzo(a)pyrene in mice has resulted in decreased survival time in the "nonresponsive" strains, DBA/2N and AKR/N (i.e., strains whose hepatic aryl hydrocarbon hydroxylase activity is not induced by PAHs when compared with corresponding controls) after 180 days. Among the "nonresponsive" strains, all of the mice in the treatment group died, with at least half the deaths occurring within 15 days of dosing. Only three mice in the "nonresponsive" control group (DBA/2N) and 6/90 (7%) of the "responsive" mice similarly exposed to benzo(a)pyrene died over the same period of time

TABLE 2-1. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Inhalation

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (mg/m^3)	LOAEL (Effect)		Reference	Chemical
					Less Serious (mg/m^3)	Serious (mg/m^3)		
CHRONIC EXPOSURE								
Cancer								
1	Hamster	109 wk 7d/wk 3-4.5 hr/d				9.5 (CEL)	Thyssen et al. 1981	BaP

mg/m^3 = milligrams per cubic meter; wk = week; hr = hour; d = day; CEL = cancer effect level; BaP = benzo(a)pyrene.

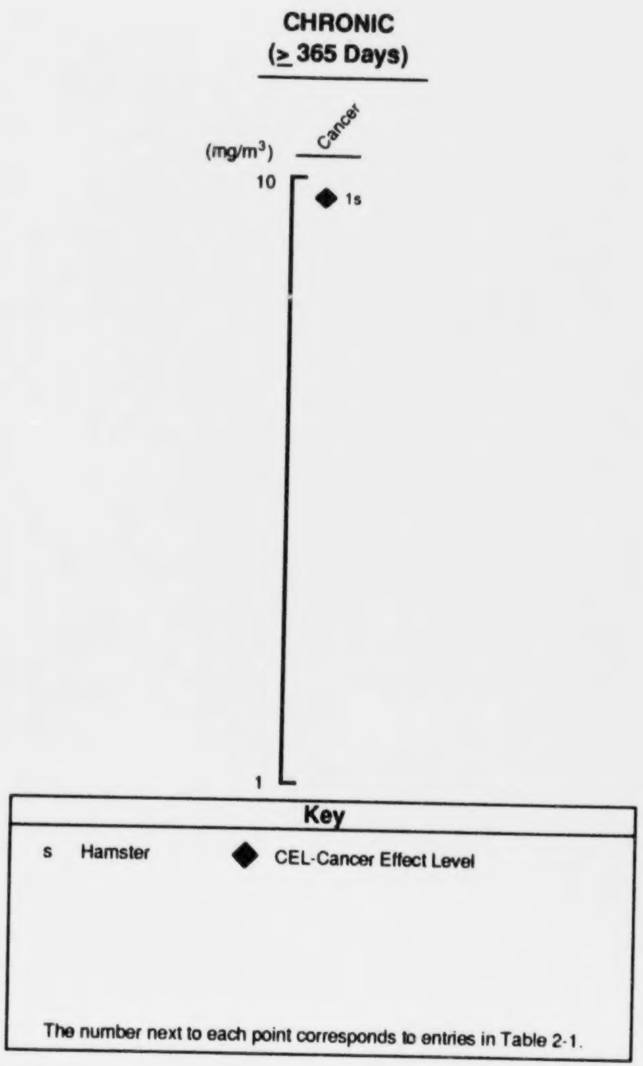


FIGURE 2-1. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Inhalation

(Robinson et al. 1975). Death appeared to be caused by bone marrow depression (aplastic anemia; pancytopenia), leading to hemorrhage or infection. The authors concluded that the decreased survival was associated with a single gene difference in aromatic hydrocarbon responsiveness. This difference is reflected in the ability to induce aryl hydrocarbon hydroxylase, an enzyme believed to be responsible for the metabolism of benzo(a)pyrene.

2.2.2.2 Systemic Effects

Gastrointestinal Effects. Minimal information is available on the gastrointestinal effects of human oral exposure to PAHs. In one study, humans that consumed anthracene-containing laxatives (the anthracene concentration was not specified) for prolonged periods of time were found to have an increased incidence of melanosis of the colon and rectum (i.e. unusual deposit of black pigments in the colon and rectum) compared to patients who did not consume anthracene laxatives. However, no definitive conclusions can be drawn from these results because of study limitations. These limitations include possible misclassification of patients with respect to anthracene laxative use over 30-years of constipation and no accounting for other factors involved in the pathogenesis of melanosis (e.g., genetics, lifestyle, other drug use etc.) (Badiali et al. 1985).

Enzyme alterations in the mucosa of the gastrointestinal tract have been observed in animals acutely exposed to anthracene, benz(a)anthracene, benzo(a)pyrene, or phenanthrene. In rats, acute intragastric administration of 50 or 150 mg/kg/day benz(a)anthracene or benzo(a)pyrene, respectively for 4 days resulted in suppressed carboxylesterase activity in the intestinal mucosa; rats exposed to 100 mg/kg/day of anthracene or phenanthrene exhibited increased carboxylesterase activity by 13% and 30%, respectively (Nousiainen et al. 1984). Enzyme alteration in the absence of other signs of gastrointestinal toxicity is not considered an adverse health effect, but it may precede the onset of more serious effects. Based on this very limited information, it would appear that acute ingestion of anthracene, benz(a)anthracene, benzo(a)pyrene or phenanthrene at these doses may not adversely affect the gastrointestinal tract of animals, however, biochemical changes were observed in exposed animals which could produce serious adverse effects at higher doses.

Hematological Effects. No studies were located regarding hematological effects in humans following oral exposure to any of the 15 PAHs discussed in this profile.

Adverse hematopoietic effects (e.g., aplastic anemia, pancytopenia) that ultimately led to death have been reported in the "nonresponsive" strains of mice, DBA/2N and AKR/N, following oral exposure to 120 mg benzo(a)pyrene/kg/day for 180 days. Death was attributed to hemorrhage or infection which resulted from pancytopenia (Robinson et al. 1975). This LOAEL is

TABLE 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Oral

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference	Chemical
ACUTE EXPOSURE									
Systemic									
1	Rat	(G)	4 d 1x/d	Gastro	150			Nousiainen et al. 1984	BaP
				Hepatic	150				
				Renal	150				
2	Rat	(G)	4 d 1x/d	Gastro	150			Nousiainen et al. 1984	BaA
				Hepatic	150				
				Renal	150				
Developmental									
3	Mouse	(G)	10 d Gd7-16		10^a		40^b (<pup weight at 20 days)	Mackenzie and Angevine 1981	BaP
4	Mouse	(F)	8 d Gd2-10				120 (fetal resorption in nonresponsive mice)	Legraverend et al. 1984	BaP
Reproductive									
5	Mouse	(G)	10 d Gd7-16		40		160 (<pregnancy maintenance)	Mackenzie and Angevine 1981	BaP
Cancer									
6	Mouse	(F)	1-7 d ad lib				33.3 (CEL)	Neal and Rigdon 1967	BaP
INTERMEDIATE EXPOSURE									
Systemic									
7	Mouse	(F)	6 mo	Hemato			120^c (aplastic anemia)	Robinson et al. 1975	BaP
				Hepatic		120 (increased liver weight)			
Reproductive									
8	Mouse	(F)	19-29 d ad lib		133.3			Rigdon and Neal 1965	BaP

TABLE 2-2 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect)		Reference	Chemical
						Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Cancer									
9	Mouse	(F)	30-197 d ad lib				2.6 (CEL)	Neal and Rigdon 1967	BaP
10	Mouse	(F)	23-238 d ad lib				33.3 (CEL)	Rigdon and Neal 1966	BaP
11	Mouse	(F)	80-140 d ad lib				33.3 (CEL)	Rigdon and Neal 1969	BaP

[a] Used to derive acute oral Minimal Risk Level (MRL); dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) resulting in an MRL of 0.1 mg/kg/day. This MRL has been converted to an equivalent concentration in food (3.6 ppm) for presentation in Table 1-3.

[b] Converted to an equivalent concentration of 308 ppm in food for presentation in Table 1-4.

[c] Converted to an equivalent concentration of 923 ppm in food for presentation in Table 1-4.

mg/kg/day = milligrams per kilogram per day; G = gavage; F = feed; d = day; x = time; Gd = gestational day; mo = months; ad lib = ad libitum; gastro = gastrointestinal; hemato = hematological; CEL = cancer effect level; < = decreased; BaP = benzo(a)pyrene; BaA = benz(a)anthracene.

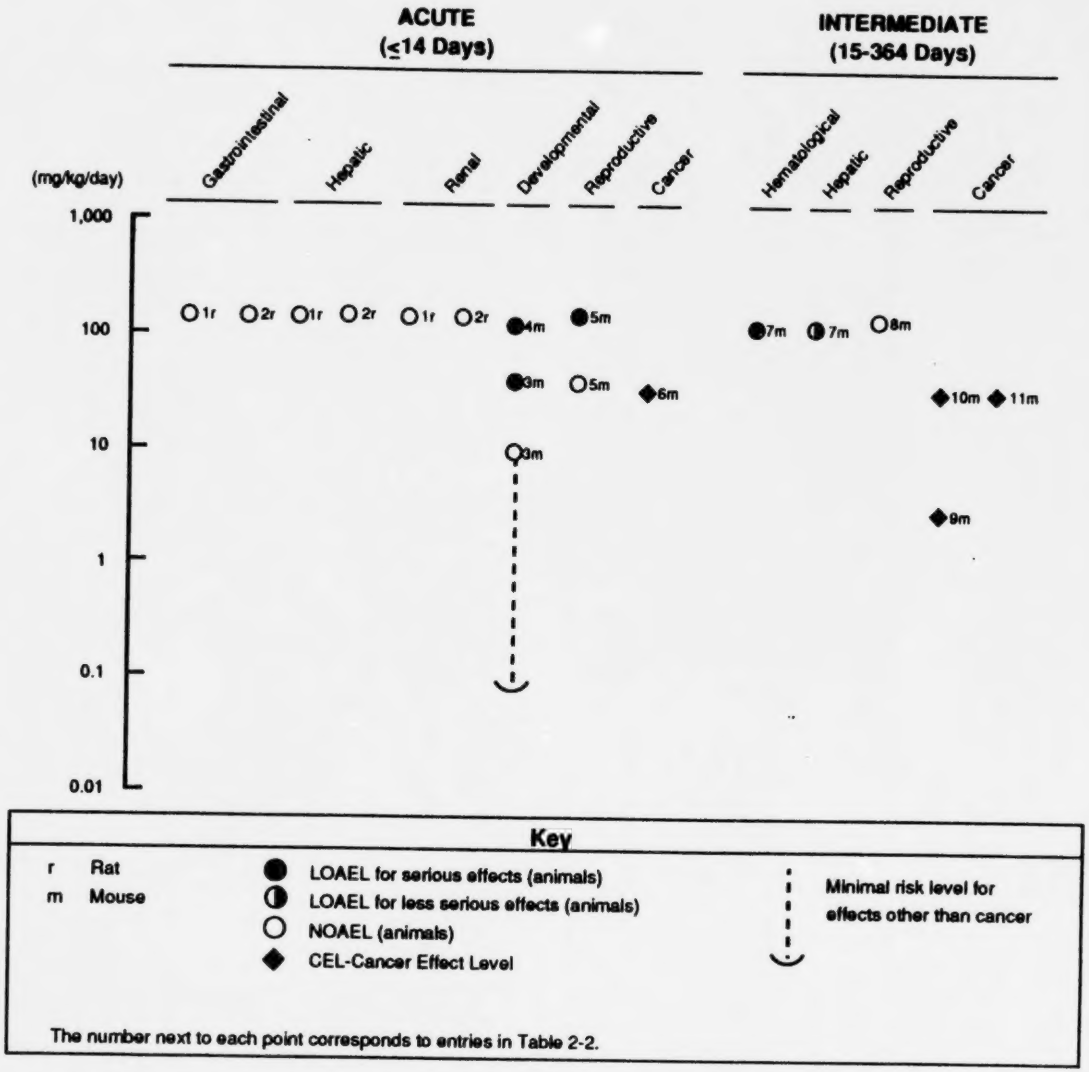


FIGURE 2-2. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Oral

presented in Table 2-2 and plotted in Figure 2-2. Similar results were obtained by Legraverend et al. (1983). Mice with a high-affinity Ah receptor (which leads to a greater induction of the cytochrome P-450 system, or "responsive" mice) administered 120 mg/kg/day benzo(a)pyrene in the diet for up to 6 months exhibited no myelotoxicity. However, low-affinity Ah receptor mice ("nonresponsive" mice) treated by the same regimen all died within three weeks due to myelotoxic effects (Legraverend et al. 1983).

Hepatic Effects. No studies were located regarding hepatic effects in humans following oral exposure to any of the 15 PAHs discussed in this profile.

The induction of preneoplastic hepatocytes, known as gamma glutamyl transpeptidase (gamma-GT) foci, in animals has been correlated with cancer promotion. A one day intragastric administration of 200 mg/kg of benzo(a)pyrene, benz(a)anthracene, or dibenz(a,h)anthracene to partially hepatectomized rats followed by a diet containing 2-acetylaminofluorene (2-AAF) and carbon tetrachloride induced gamma-GT foci (Tsuda and Farber 1980). Benzo(a)pyrene was a more potent foci inducer than either benz(a)anthracene or dibenz(a,h)anthracene

The ability to induce aldehyde dehydrogenase (ADH) in animals has also been correlated with carcinogenic potency. Rats intragastrically administered 100 mg/kg/day of benzo(a)pyrene, benz(a)anthracene, anthracene, chrysene, or phenanthrene for 4 days exhibited cytosolic aldehyde dehydrogenase (ADH) induction (Torronen et al. 1981). However, benzo(a)pyrene and benz(a)-anthracene were much more effective than phenanthrene, chrysene, and anthracene. Exposure to benzo(a)pyrene and benz(a)anthracene also increased the relative liver weights by 27 and 19%, respectively (Torronen et al. 1981). The authors concluded that anthracene, phenanthrene, and chrysene, which have been characterized as either non-carcinogens or equivocal carcinogens (see Section 2.2.2.8), are poor ADH inducers (Torronen et al. 1981).

The induction of carboxylesterase activity has also been observed in animals exposed to PAHs (Nousiainen et al. 1984). Benzo(a)pyrene, benz(a)anthracene and chrysene are moderate inducers of hepatic carboxylesterase activity in rats intragastrically administered 50, 100, 150 mg/kg/day, respectively for 4 days. However, rats administered 100 mg/kg/day anthracene or phenanthrene did not exhibit induction of hepatic carboxylesterase activity.

The extent of liver regeneration, which is indicative of the ability to induce a proliferative response, has also been examined following acute oral exposure to various PAHs. Partially hepatectomized rats were fed diets containing various PAHs for 10 days. Administration of 51.4 mg/kg/day acenaphthene or 180 mg/kg/day of fluorene resulted in a statistically significant increase in the extent of liver regeneration, while 15.4 mg/kg/day acenaphthene, 51.4 mg/kg/day benzo(a)pyrene, and 514 mg/kg/day pyrene, anthracene or phenanthracene had no effect on the extent of liver regeneration. Diets containing 51.4 mg/kg/day acenaphthene or dibenz(a,h)anthracene, 180 mg/kg/day anthracene or phenanthracene or 437 mg/kg/day pyrene produced no increase in the liver-to-body-weight ratio. Rats fed a diet containing 514 mg/kg/day chrysene exhibited equivocal results, in one trial a significant increase in liver regeneration was noted, while in another trial no increase in liver regeneration of liver-to-body-weight ratio was observed (Gershbein 1975). Thus, both suspected carcinogenic and noncarcinogenic PAHs stimulate liver regeneration, although much higher doses are required for noncarcinogenic PAHs.

Subchronic oral administration of pyrene to rats in their diet produced enlarged and fatty appearing livers (White and White 1939). "Nonresponsive" strains of mice (i.e. those incapable of producing increased levels of cytochrome P-450 enzymes in response to benzo(a)pyrene exposure) (C57Bl/6, C3H/HeN, BALB/cAnN) orally administered 120 mg benzo(a)pyrene kg/day in their diet for 180 days exhibited increased relative liver weights (Robinson et al. 1975).

Thus, the hepatic effects observed in animals following oral exposure are generally not considered serious. However the enzyme alterations, gamma-GT foci induction, liver regeneration and increased liver weight may precede the onset of more serious hepatic effects.

The highest NOAEL values and one reliable LOAEL value for hepatic effects in mice and rats for acute and intermediate exposure are recorded in Table 2-2 and plotted in Figure 2-2.

Renal Effects. The kidney microsomal carboxylesterase activity of rats was moderately induced by 50-150 mg/kg of benzo(a)pyrene following 4 days of intragastric administration; however, rats administered 100 mg/kg/day of anthracene or phenanthrene did not exhibit increased activity. The authors conclude that anthracene and phenanthrene are non-inducers of kidney carboxylesterase activity (Nousiainen et al. 1984). Enzyme induction in the absence of other signs of renal toxicity is not considered an adverse health effect, but it may precede the onset of more serious effects, such as impaired renal function and/or irreversible histopathologic changes.

Mice administered increasing dietary doses of pyrene ranging from 1,000 mg/kg food (127 mg/kg/day) up to 25,000 mg/kg food (917 mg/kg/day) over a 25 day study exhibited dilation of the renal tubules in an unspecified number of mice. These effects were not observed until the highest dose was administered (Rigdon and Giannukos 1964). The limitations of this study (e.g. doses changed throughout exposure period and no statistical analyses were performed) render these results of questionable toxicological significance.

The highest NOAEL values for renal effects in rats following acute duration exposure are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals following oral exposure to the 15 PAHs discussed in this profile.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals following oral exposure to the 15 PAHs discussed in this profile.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to PAHs. Three animal studies were reviewed that detected developmental effects of benzo(a)pyrene in inbred strains of rats and mice. The data from these studies indicate that prenatal exposure to benzo(a)pyrene produced reduced mean pup weight during postnatal development and a high incidence of sterility in the F1 progeny of mice (Mackenzie and Angevine 1981). Using aromatic hydrocarbon (Ah)-responsive and non-responsive strains of mice, the increased incidence of stillborns, resorptions and malformations observed were directly related to the maternal and/or embryonal genotype (Legraverend et al. 1984). In rats, effects were reported following benzo(a)pyrene treatment during gestation (Sheveleva 1978). No more details were available for this study. However, in a fourth study, negative results were obtained when benzo(a)pyrene was administered to mice (Rigdon and Neal 1965).

Benzo(a)pyrene was administered by gavage to pregnant CD-1 mice during gestation at doses of 10, 40 and 160 mg/kg/day. The viability of litters at parturition was significantly reduced in the highest dose group (Mackenzie and Angevine 1981). The mean pup weight was significantly reduced in all treatment groups by 42 days of age. The F1 progeny that were exposed prenatally to benzo(a)pyrene (10, 40, and 160 mg/kg/day) were bred with untreated animals and further studied for postnatal development and reproductive function. The F1 progeny from the 10 mg/kg/day group experienced decreased fertility with associated alterations in gonadal morphology and germ-cell development. Since only the parental doses are quantifiable, these are the only data presented in Table 2-2. Therefore, the LOAEL of 10 mg/kg/day noted in the F1 progeny discussed above is not presented in Table 2-2. Higher doses produced total sterility. This well conducted study provides good evidence for the occurrence of developmental effects following *in utero* exposure to benzo(a)pyrene.

Daily dietary administration of 120 mg/kg/day benzo(a)pyrene from day 2 to 10 of gestation to Ah-nonresponsive AKR/J mice (Ah^d/Ah^d) bred to Ah-responsive C57BL/6N mice (Ah^b/Ah^b) produced more stillborns, resorptions and malformations in Ah^d/Ah^d than Ah^b/Ah^d embryos (Legraverend et al. 1984). No such differences were seen in genetically different litter mates from Ah-responsive $B6AKF_1$ mothers. These differences were attributed to the metabolic differences in these strains resulting from "first pass" liver metabolism occurring upon dietary intake of benzo(a)pyrene. Thus, the authors felt that both maternal as well as target organ metabolism (embryo/fetus) was important in determining susceptibility to developmental toxicity. Although this was a well designed study, use of a single dosage level (120 mg/kg/day) precluded assessment of dose-response.

In another study, negative results were obtained when the potential developmental effects of benzo(a)pyrene were studied in mice (Rigdon and Neal 1965). Dietary administration of this chemical to mice at concentrations equivalent to 33.3, 66.7, or 133.3 mg/kg/day at various times before and after mating elicited no adverse effects on the developing embryos and no malformations were observed. Maternal weight gain was reduced in the mice administered the higher levels of benzo(a)pyrene (1,2, and 3 ppm), but this effect was reversed when the animals were changed to the control ration. Limitations of this study that preclude its inclusion in Table 2-2 consist of the use of an inconsistent protocol, varying number of animals, and varying time of gestation exposure.

The highest NOAEL values and all reliable LOAEL values for developmental effects in mice for acute exposure duration is reported in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to PAH compounds. Only three animal studies were located which evaluated the reproductive effects of benzo(a)pyrene in animals; no studies were located on other PAH compounds. The results of two oral studies in mice (Mackenzie and Angevine 1981; Rigdon and Neal 1965) and one in rats (Rigdon and Rennels 1964) indicate that benzo(a)pyrene induces reproductive toxicity in animals. The incidence and severity of these effects depends on the strain, method of administration and dose levels used. In a two-generation study, benzo(a)pyrene administered by gavage to pregnant CD-1 mice decreased the percentage of pregnant females at parturition and produced a high incidence of sterility in the progeny (Mackenzie and Angevine 1981). In contrast, benzo(a)pyrene administered in the diet caused no adverse effects on fertility of Swiss mice (Rigdon and Neal 1965), but reduced the incidence of pregnancy in female rats (Rigdon and Rennels 1964). Based on these studies, the LOAEL for benzo(a)pyrene-induced reproductive toxicity in parental mice was 160 mg/kg/day and the LOAEL for these effects in the progeny of exposed animals was 10 mg/kg/day (Mackenzie and Angevine 1981). Since only the parental doses are quantifiable, these are the only data presented in Table 2-2. No NOAEL was identified.

CD-1 mice receiving benzo(a)pyrene by gavage daily for 10 days during gestation exhibited a significant reduction in the percentage of pregnant females at parturition at 160 mg/kg/day, the highest dose tested (Mackenzie and Angevine 1981). When F1 progeny were bred with untreated animals, the fertility index decreased significantly in all treatment groups. At 10 mg/kg/day, the lowest dose tested, reduced fertility noted in the animals was associated with significant alterations in gonadal morphology and germ cell development. The treatment at higher doses resulted in total sterility. Contrary to these results, no adverse effects on reproduction were observed in Swiss mice fed benzo(a)pyrene in the diet up to concentrations equivalent to 133 mg/kg/day over varying time spans during mating, gestation and parturition (Rigdon and Neal 1965). The apparent discrepancy in the results of the two studies may be attributed to the method of benzo(a)pyrene administration and metabolic differences in the two strains of mice used.

Dietary administration of benzo(a)pyrene for 28 days revealed no treatment-related effects on the estrus cycle of female rats. These rats experienced no significant adverse effects on their fertility when bred to untreated male rats (Rigdon and Rennels 1964). In another series of experiments, when benzo(a)pyrene fed male and female rats were bred, only two of seven females were pregnant; one rat had stillborns and others had resorptions (Rigdon and Rennels 1964). Although the data suggest that benzo(a)pyrene may induce reproductive toxicity in rats, they are inconclusive because of the use of a single dose level and inadequate reporting of data.

The available information from animal studies suggests that benzo(a)pyrene may have the potential to produce adverse reproductive effects in exposed humans. The highest NOAEL and all reliable LOAEL values for reproductive effects following acute intermediate duration exposures in mice is reported in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans following oral exposure to PAHs. Oral exposure to a total dose of 10 mg/kg benzo(a)pyrene produced gene mutations in mice in the mouse coat color spot test (Davidson and Dawson 1976, 1977). Orally administered fluoranthene (400 and 750 mg/kg) did not increase the sister chromatid exchange frequency in mice (Palitti et al. 1986). Gene mutations were not produced in bacteria or yeast in a host-mediated assay in which anthracene, benzo(a)pyrene, chrysene or fluoranthene were administered to mice by gavage; positive results were produced in bacteria in the same test system in which mice were exposed to benz(a)anthracene and injected intraperitoneally with the bacteria (Simmon et al. 1979).

2.2.2.8 Cancer

No studies were located regarding cancer in humans following oral exposure to the 15 PAHs discussed in this profile. The animal studies discussed in this section are presented first by exposure duration (acute, intermediate and chronic) and within each duration category the information on individual PAHs is discussed in alphabetical order. Those PAHs for which no information was available for specified exposure durations were omitted.

Acute-Duration Exposure

Mice acutely administered 2 mg benz(a)anthracene by oral gavage for 2 days exhibited increased incidences of hepatomas and pulmonary adenomas (80% and 85%, respectively) after 568 days of observation, when compared to controls (Klein 1963). No malignant tumors were observed in this study. However, a single gavage administration of 0.5 mg benz(a)anthracene produced no tumors in mice after 68 weeks. Multiple gavage administration resulted in the occurrence of forestomach papillomas in 7% of the animals compared to none in the controls (Bock and King 1959).

A relationship between the ingestion of benzo(a)pyrene at doses that range from 1.5 to 400 mg/kg/day and the development of benign and malignant tumors of the forestomach has been documented in several studies in mice (Hartwell 1951; Shubik and Hartwell 1957; Thompson 1971; Tracor/Jitco 1973a, 1973b). Acute intragastric doses of 50-67 mg/kg benzo(a)pyrene have also been shown to elicit pulmonary adenomas and forestomach papillomas in mice (Sparnins et al. 1986; Wattenberg and Bueding 1986; Wattenberg and Leong 1970). Intermittent gavage exposure of mice to 50-67 mg/kg benzo(a)pyrene resulted in increased forestomach (100%) and pulmonary tumor incidences at 30 weeks of age (Sparnins et al. 1986; Wattenberg and Leong 1970), however, no controls were included. Mice fed benzo(a)pyrene in the diet at concentrations equivalent to 33.3 mg/kg/day exhibited gastric neoplasms following 2 or more days of consumption. However, lower concentrations of benzo(a)pyrene (equivalent to 13.3 mg/kg/day) administered for up to 7 days did not produce forestomach tumors (Neal and Rigdon 1967, see Table 2-2). Hamsters have also been observed to develop papillomas and carcinomas of the alimentary tract in response to gavage or dietary exposure to benzo(a)pyrene (Chu and Malmgrem 1965). An extremely large single oral dose of 100 mg benzo(a)pyrene (200 mg/kg) induced mammary tumors in 88% of female Sprague-Dawley rats (Huggins and Yang 1962). Similarly, a 77% mammary tumor incidence was observed 90 weeks after a single oral dose of 50 mg benzo(a)pyrene (100 mg/kg) was administered to rats, as compared to a 30% incidence in untreated animals (McCormick 1981).

A single dose of 0.05 mg/kg dibenz(a,h)anthracene in PEG-400 produced forestomach papillomas in 5% of male Swiss mice after 30 weeks (Berenblum and Haran 1955).

A single oral dose of 400 mg/kg phenanthrene to Sprague-Dawley rats produced no mammary tumors within 60 days (Huggins and Yang 1962).

Intermediate-Duration Exposure

Two subchronic studies were located in which benz(a)anthracene was administered by gavage which provide evidence of its carcinogenic potential. Mice that received intermittent doses of 1.5 mg/kg/day benz(a)anthracene for 5 weeks (Klein 1963) or for unspecified intermediate lengths of time (Bock and King 1959) exhibited significantly elevated incidences of hepatomas and lung adenomas following up to 60 days of observation (Klein 1963). Neither of these studies were adequately reported; they did not include complete histopathology, adequate treatment durations, large enough sample sizes or statistical analysis. In addition, the authors did not determine whether benz(a)anthracene produced malignant tumors. Thus, although these studies are inconclusive because of methodological limitations, they do provide some qualitative evidence for the potential carcinogenicity of benz(a)anthracene by the oral route.

The incidence of forestomach tumors (papillomas and carcinomas) was related to the duration of oral exposure to benzo(a)pyrene following subchronic administration of dietary benzo(a)pyrene at various doses up to 250 ppm (33.3 mg/kg/day) for 30 to 197 days to mice (Neal and Rigdon 1967, see Table 2-2). The tumor incidence increased with increasing dose. In the same study mice fed 250 ppm (33 mg/kg/day) for periods of 1 to 7 days exhibited increased forestomach tumor incidences following 2 or more days of benz(a)pyrene exposure (total dose of 2 mg), while mice fed 10 ppm (13.3 mg/kg/day) for 110 days (total dose of 4.48 mg) did not develop tumors. The authors suggest that these findings provide evidence that there are no cumulative carcinogenic effects of benzo(a)pyrene or its metabolites in mice. This study provides the best dose-response information available for the oral route of exposure, despite the irregular protocol employed, although the relevance of forestomach tumors in rodents to human cancer is the subject of some controversy.

An association between dietary benzo(a)pyrene and the development of leukemia and forestomach and lung tumors has been observed in mice. Tumor incidence was related to both dose and length of exposure (except in the case of leukemia). Mice administered dietary doses of up to 1,000 ppm (up to 133 mg/kg/day) for intermediate lengths of time (38-238 days) exhibited an increased incidence of stomach tumors (papillomas and carcinomas) (Rigdon and Neal 1966, 1969, see Table 2-2). Mice administered 250 ppm (33.3 mg/kg/day) benzo(a)pyrene developed papillomas or carcinomas of the stomach (64%) and all the mice in the 1000 ppm (133 mg/kg/day) group exhibited gastric tumors after 86 days of benzo(a)pyrene consumption. A similar relationship was observed for the incidence of lung tumors, as mice fed 250 ppm (33.3 mg/kg/day) benzo(a)pyrene exhibited an increased lung adenoma incidence. The occurrence of leukemia was related to the ingestion of 250 ppm (33.3 mg/kg/day) benzo(a)pyrene; 37% of the treated mice developed leukemias (Rigdon and Neal 1969, see Table 2-2). The lack of consistent protocol in these experiments, and the short exposure duration and observation periods, preclude the assessment of a dose-response relationship. Furthermore, tumors were reported as combined papillomas and carcinomas, so that no distinction between these benign and malignant tumors can be made.

Mammary tumors have also been observed following intermediate duration exposure to benzo(a)pyrene in rats. Eight weekly oral doses of 6.25 mg benzo(a)pyrene (12.5 mg/kg) administered to rats resulted in a 67% increase in the incidence of mammary tumors in female rats after 90 weeks of observation (McCormick 1981). A 30% incidence in these tumors was observed in the control animals. Therefore, this study was not included in Table 2-2 or Figure 2-2.

Several subchronic studies that investigated the carcinogenicity of dibenz(a,h)anthracene in animals following oral exposure via the diet or drinking water were located. Mammary carcinomas were observed in 5% of the female BALB/c mice dosed with 0.5% dibenz(a,h)anthracene after 15 weeks, however, no control group was included (Biancifiori and Caschera 1962). Mice (strain unspecified) receiving dibenz(a,h)anthracene in the diet for 5 to 7 months developed forestomach tumors in 32% of animals surviving at 1 year (Larinow and Soboleva 1938). None of these studies was adequately reported: they did not perform appropriate histopathologic evaluations, treatment or study durations were inadequate, the sample size was inadequate and the relevance of forestomach tumors in rodents to human cancer is the subject of some controversy. Despite these methodological limitations, these studies do provide some evidence of dibenz(a,h)anthracene's carcinogenicity by the oral route. Therefore, these studies were not included in Table 2-2 and Figure 2-2.

Subchronic dietary administration of fluorene to rats for 6 months at a concentration approximately equivalent to 8.6 mg/kg/day produced increased incidences of squamous cell carcinoma of the kidney and uterus (9% and 9%, respectively). However, control animals exhibited a 5% increase in the incidence of kidney adenoma, 11% increase in the incidence of pituitary adenoma, and 5% increase in the incidence of granulocytic leukemia (Morris et al. 1960). The presence of tumors in control animals render these results difficult to interpret. Therefore, these studies were not included in Table 2-2 and Figure 2-2.

Chronic-Duration Exposure

Chronic oral administration of a total dose of 4.5 g/rat anthracene in the diet to BD1 or B111 rats for 78 weeks did not produce tumors (Druckrey and Schmahl 1955) Thus, the results of this one study suggest that anthracene is noncarcinogenic in animals following chronic oral exposure.

Mice of various strains that received dibenz(a,h)anthracene emulsions in mineral oil or olive oil in place of drinking water at a dose approximately equal to 25 mg/kg/day throughout their lifetimes developed lung adenomas and papillomas and squamous cell carcinomas of the forestomach (Lorenz and Stewart 1948; Snell and Stewart 1962, 1963). However, extensive dehydration and emaciation occurred since the animals did not tolerate the vehicle well, leading to early death and the need to periodically remove the animals from the treatment vehicle.

These results indicate that benz(a)anthracene, benzo(a)pyrene, and dibenz(a,h)anthracene, and possibly other PAHs, are potentially carcinogenic following oral exposure. Thus, humans exposed to benzo(a)pyrene, benz(a)anthracene, and dibenz(a,h)anthracene in areas surrounding hazardous waste sites may be at risk of developing cancer, particularly in the liver, mammary gland and respiratory and gastrointestinal tracts.

All reliable cancer effect levels (CELs) in mice for acute and intermediate exposure durations are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.3 Dermal Exposure

No studies were located regarding effects in humans following dermal exposure to the 15 PAHs discussed in this profile.

Table 2-3 describes the health effects observed in laboratory animals associated with dermal exposure at varying times and exposure durations.

2.2.3.1 Death

No studies were located regarding death in humans or animals following dermal exposure to the 15 PAHs discussed in this profile.

2.2.3.2 Systemic Effects

Dermal Effects. The carcinogenic PAHs as a group cause skin disorders; however, specific effects of individual PAHs, except for benzo(a)pyrene have not been reported.

Regressive verrucae was reported following up to 120 dermal applications of 1% benzo(a)pyrene to human skin over 4 months (Cottini and Mazzone 1939). Although reversible and apparently benign, the changes were thought to represent neoplastic proliferation. This study is flawed in that no benzene control was evaluated. Similar epidermal changes were reported by Rhoads et al. (1954) in humans exposed to benzo(a)pyrene. Human volunteers were painted daily for 4 consecutive days on 1 cm^2 areas of the upper back. Nucleolar enlargement was observed (Rhoads et al. 1954).

Adverse dermal effects have been noted in humans following subchronic dermal exposure to benzo(a)pyrene in patients with preexisting dermal conditions of pemphigus vulgaris and xeroderma pigmentosum (Cottini and Mazzone 1939). A 1% benzo(a)pyrene solution topically applied to patients with pemphigus resulted in local bullous eruptions characteristic of the disease. Patients with xeroderma pigmentosum exposed to 1% benzo(a)pyrene slightly longer exhibited only pigmentary and slight verrucous effects. Patients with preexisting active skin lesions due to squamous cell cancer similarly treated showed a general improvement and/or retardation of the lesion. The severity of abnormal skin lesions appeared to be related to age as those in the lowest age range exhibited fewer and less severe effects than those in the mid-range groups. No such age relationship of effects involving those patients with normal or preexisting skin lesions was noted.

Adverse dermal effects have also been observed in animals following both acute and intermediate-duration dermal exposure to various PAHs. In a number of older investigations, acute topical application of various PAHs has been reported to suppress or destroy sebaceous glands in mouse skin (e.g., Bock and Mund 1958). Benzo(a)pyrene, benz(a)anthracene or dibenz(a,h)anthracene applied to the shaved backs of Swiss mice were all reported to suppress sebaceous glands (Bock and Mund 1958). However, controls were not employed; therefore, it is not possible to determine if the effects seen were due to the solvent and/or the application procedures.

It has been suggested that an increase in the number of skin melanocytes correlates with the sebaceous gland suppression index, and that the short term melanocyte-activation test is useful for the detection of skin carcinogens and promoters. Some chemical carcinogens have been shown to induce melanogenesis in melanoblasts in the skin. Anthracene, benzo(a)pyrene, chrysene, fluoranthene, fluorene or pyrene were examined for their ability to induce melanocyte activation by topical application to the backs of mice for 1 or 2 consecutive days. Benzo(a)pyrene, an animal skin carcinogen, was a potent melanocyte inducer at doses of 20-100 μg/mouse (0.005-0.025 mg/cm^2) as demonstrated by an increase of up to 19 times over controls in the number of dopa-positive cells, whereas no effects were seen at 4 μg/mouse (0.001 mg/cm^2). Chrysene, a weak skin carcinogen (in animals), increased the number of dopa-positive cells 4 times that of controls following an application of 50 μg/mouse (0.0125 mg/cm^2), while larger doses did not cause further increases in the numbers of these cells. Other PAHs such as anthracene, fluoranthene, fluorene or pyrene (PAHs that are considered to be noncarcinogenic) produced no increases in the number of active melanocytes when applied at a dose of 200 μg/mouse (0.05 mg/cm^2) (Iwata et al. 1981).

An acute (96-hour) dermal application of anthracene to the backs of hairless mice followed by ultraviolet radiation (UVR) exposure for 40 minutes resulted in enhanced dermal inflammation compared to mice exposed exclusively to UVR. However, this effect was reversed within 48 hours (Forbes et al.

TABLE 2-3. Levels of Significant Exposure to Polycyclic Aromatic Hydrocarbons - Dermal

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL	LOAEL (Effect)		Reference	Chemical
					Less Serious	Serious		
ACUTE EXPOSURE								
Systemic								
1	Mouse	1-2 d 1x/d	Derm/Oc	0.05 mg/cm^2			Iwata et al. 1981	pyrene
2	Mouse	1-2 d 1x/d	Derm/Oc	0.05 mg/cm^2			Iwata et al. 1981	fluora
3	Mouse	1-2 d 1x/d	Derm/Oc		0.0125 mg/cm^2 (slight increase melanocytes)		Iwata et al. 1981	chrys
4	Mouse	1-2 d 1x/d	Derm/Oc	0.05 mg/cm^2			Iwata et al. 1981	fluor
5	Mouse	1-2 d 1x/d	Derm/Oc	0.05 mg/cm^2			Iwata et al. 1981	anthra
6	Mouse	1-2 d 1x/d	Derm/Oc	0.001 mg/cm^2	0.005 mg/cm^2 (induction of melanocytes)	0.025 mg/cm^2 (substantial melanocytes)	Iwata et al. 1981	BaP
Immunological								
7	Mouse	5 d 2x/5d			120 ug (contact hyper-sensitivity)		Klemme et al. 1987	BaP
INTERMEDIATE EXPOSURE								
Immunological								
8	Gn Pig	2-3 wk 2x			0.001 % (slight contact sensitivity)	1.0% (contact sensitivity)	Old et al. 1963	BaP
Cancer								
9	Mouse	1 d 1x/d then 23 wk 2d/wk (TPA)				0.0054 mg/kg/day (CEL tumor initiation)	Cavalieri et al. 1988b	BaP

TABLE 2-3 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL	LOAEL (Effect)		Reference	Chemical
					Less Serious	Serious		
10	Mouse	1 d 1x/d then 25 wk 3d/wk (TPA)				0.57 (CEL) mg (total dose)	Levin et al. 1984	BaA
11	Mouse	20 d 1x/2d then 22 wks (TPA)				100 (CEL tumor ug initiation) (total dose)	Rice et al. 1985a	indp
12	Mouse	20 wk 2d/wk 1x/d				0.025 (CEL) mg (total dose)	Cavalieri et al. 1988b	BaP
CHRONIC EXPOSURE								
Cancer								
13	Mouse	lifetime 3d/wk 1x/d				0.1% (CEL)	Wynder and Hoffmann 1959b	BbF
14	Mouse	17-22 mo 2d/wk 1x/d				2 (CEL) ug (total dose)	Habs et al. 1984	BaP
15	Mouse	99 wk 2d/wk 1x/d				12.5 (CEL) ug (total dose)	Warshawsky and Barkley 1987	BaP

d = day; x = time; wk = week; mo = months; ug = micrograms; mg = milligrams; derm/oc = dermal/ocular; CEL = cancer effect level; anthra = anthracene; BaP = benzo(a)pyrene; BbF = benzo(b)fluoranthene; chrys = chrysene; BaA = benzo(a)anthracene; fluor = fluorene; fluora = fluoranthene; indp = indeno(1,2,3-cd)pyrene; mix = mixed PAHs; TPA = tetradecanoyl phorbol acetate.

1976). Anthracene thus potentiates the skin damage elicited by sunlight exposure and may be considered a photosensitizer in hairless mice. This may be important to humans dermally exposed to anthracene from nearby hazardous waste sites in conjunction with sunlight.

In animals, dermal application of 1% benzo(a)pyrene to the skin of hairless mice resulted in epidermal cell growth alterations (Eljo 1968). Increases in mitotic rates, mitotic counts, and mitotic duration that, according to the author, were indicative of a regenerative reaction were observed. However, concurrent controls were not utilized. The authors concluded that the alterations in the kinetics of epidermal cell growth produced by benzo(a)pyrene were more sustained than after application of croton oil. The study is limited for drawing conclusions concerning the dermal toxicity of benzo(a)pyrene in that experimental data were compared with historical controls only, no acetone-control was evaluated and the statistical significance of the increased values was not determined. The toxicological significance of these effects is questionable for the reason listed above.

All reliable LOAEL values for dermal effects in mice and guinea pigs for acute and intermediate exposure durations are recorded in Table 2-3.

2.2.3.3 Immunological Effects

No studies were located regarding immunological effects in humans following dermal exposure to the 15 PAHs discussed in this profile.

Benzo(a)pyrene is immunogenic when applied dermally to the skin of animals. In mice, acute application of 120 μg benzo(a)pyrene elicited an allergic contact hypersensitivity in C3H mice which was antigen specific (Klemme et al. 1987). Slight contact hypersensitivity was also observed in guinea pigs following two dermal applications of 0.001% benzo(a)pyrene given over a period of 2-3 weeks. This response was more severe at a dose of 1.0% benzo(a)pyrene (Old et al. 1963). These data are presented in Table 2-3.

No studies were located regarding the following health effects in animals following dermal exposure to the other PAHs discussed in this profile.

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans following dermal exposure to PAHs. A single topical application of 100 μg benzo(b)-

fluoranthene, benzo(k)fluoranthene, or indeno(1,2,3-c,d)pyrene (Weyand et al. 1987) was reported to bind to DNA in CD-1 mouse skin following dermal exposure. The relative extent of binding was benzo(b)fluoranthene > benzo(k)fluoranthene > indeno(1,2,3-cd)pyrene (Weyand et al. 1987). Covalent binding of chemicals to DNA can result in strand breaks and DNA damage, ultimately leading to mutations.

2.2.3.8 Cancer

No studies were located that gave evidence of a direct association between human dermal exposure to individual PAHs and cancer induction. However, reports of skin tumors among individuals exposed to mixtures containing PAHs lend some qualitative support to their potential for carcinogenicity in humans. The earliest of these is the report by Pott (1775) of scrotal cancer among chimney sweeps. More recently, skin cancer among those dermally exposed to shale oils has been reported (Purde and Etlin 1980). However, these reports provide only qualitative suggestions pertaining to the human carcinogenic potential of all of the 15 PAHs discussed in this profile, or at least the compounds found in chimneys and shale oils, such as benzo(a)pyrene, chrysene, dibenz(a,h)anthracene, benz(a)anthracene, or benzo(b)fluoranthene. Limitations in these reports include no quantification of exposure to individual PAHs and concurrent exposure to other putative carcinogens in the mixtures.

Complete Carcinogenesis Studies

Studies in laboratory animals have demonstrated the ability of benz(a)anthracene, benzo(b)fluoranthene, benzo(a)pyrene, chrysene, dibenz(a,h)anthracene, and indeno(1,2,3-cd)pyrene to induce skin tumors (i.e. they are complete carcinogens) following intermediate dermal exposure. Anthracene, fluoranthene, fluorene, phenanthrene, and pyrene do not act as complete carcinogens. The data supporting these conclusions are discussed below by chemical. Only those studies considered adequate and reliable are presented in Table 2-3.

Anthracene. Anthracene was negative as a complete carcinogen following chronic dermal exposure (Habs et al. 1980). Swiss mice receiving 10% anthracene in acetone topically applied to their backs three times a week throughout their lifetime did not develop any skin tumors after 20 months. (Wynder and Hoffmann 1959a). However, in the same study, smaller concentrations of chrysene (1%), benzo(a)pyrene (0.001%) and dibenz(a,h)-anthracene (0.001%) elicited tumor induction within a year (Wynder and Hoffman 1959a).

Benz(a)anthracene. Benz(a)anthracene has been shown to cause skin tumors in mice following intermediate duration dermal application. Topically applied graded concentrations of benz(a)anthracene in toluene or n-dodecane to the backs of mice for 50 weeks resulted in dose-related increases in tumor incidence (Bingham and Falk 1969). This response was enhanced when n-dodecane was the solvent compared with toluene. Malignant tumors were observed at dose levels of about 0.02% benz(a)anthracene (0.15 mg/kg/day) and above when toluene was the solvent; however, when n-dodecane was the solvent tumors were observed at much lower concentrations of 0.0002% benz(a)anthracene (0.0015 mg/kg/day). The dose-response relationship reported in this study is extremely shallow (sublinear) over 2 orders-of-magnitude. The biologically active dose at the target site (reactive form of the agent at the site of action) is not directly proportional to administered dose at the high doses employed. This may be due to mechanisms of interaction such as saturation of metabolic activating systems. No solvent controls were included for comparison (Bingham and Falk 1969).

Intermediate duration topical application of benz(a)anthracene to the backs of mice for 30 weeks resulted in a slightly elevated (2.6%) skin tumor incidence. No definitive conclusions can be drawn from this study since only one dose was employed and no statistical analysis was performed. In the same study, nearly equivalent doses of benzo(a)pyrene similarly administered produced an increased skin tumor incidence of 79%; decreased survival and tumor latency were also noted (Cavalieri et al. 1977).

Benzo(b)fluoranthene. A dose-response relationship for the dermal carcinogenicity of benzo(b)fluoranthene has been demonstrated over an order-of-magnitude dose range in Swiss mice receiving (0.01 to 0.5%) benzo(b)-fluoranthene throughout their lifetime. Survival was also dose-related. Although this study was designed as a long-term (chronic) bioassay, malignant tumors (90% carcinomas) appeared as early as 4 months in the high-dose benzo(b)fluoranthene group. Papillomas and carcinomas (65 and 85%, respectively) also appeared after 5 months in the intermediate-dose, benzo(b)fluoranthene group. As a result, this study provides evidence that benzo(b)fluoranthene is carcinogenic following intermediate-duration exposure. The lowest dose at which benzo(b)fluoranthene elicited malignant tumors was 0.1%, which is approximately equal to a dose of 2.9 mg/kg received three times weekly, or an average daily dose of 1.2 mg/kg (Wynder and Hoffmann 1959b, see Table 2-3). In another chronic dermal study benzo(b)fluoranthene produced a significant carcinogenic response at approximately one-third the potency of benzo(a)pyrene. The lowest dose at which tumors appeared was 3.4 μg benzo(b)fluoranthene, however, no distinction was made between papillomas and carcinomas, and this strain of NMRI mice has exhibited a high background incidence of systemic tumors (Habs et al. 1980).

Benzo(a)pyrene. Benzo(a)pyrene is a potent experimental skin carcinogen, and it is often used as a positive control in bioassays of other agents. Benzo(a)pyrene was first reported to induce skin tumors in mice in 1933 (Cook et al. 1933; Cook 1933), although mixtures of PAHs that include benzo(a)pyrene such as coal tar were shown to be dermal carcinogens in animals as early as 1918 (Yamagiwa and Ichikawa 1918). In its role as a positive control, benzo(a)pyrene is usually administered at a single dose level, so that quantitative evaluation of dose-response relationships is not possible.

Subchronic (19-20 weeks) topical application of a benzo(a)pyrene solution to the backs of mice resulted in a dose-related development of skin papillomas and squamous cell carcinomas (Cavalieri et al. 1988b, see Table 2-3; Shubik and Porta 1957). In mice, the tumorigenic dose of benzo(a)pyrene is influenced by the solvent used for delivery. Graded concentrations of benzo(a)pyrene dissolved in decalin or a solution of n-dodecane and decalin were topically administered to the backs of mice for 50 weeks (Bingham and Falk 1969). Use of the n-dodecane and decalin solvent mixture significantly enhanced the potency of benzo(a)pyrene at lower doses in comparison with decalin alone. Malignant tumors appeared in 21% of the animals at 0.00002% (0.0054 mg/kg/day) benzo(a)pyrene in dodecane and decalin solvent. In contrast, a 42% skin tumor incidence was not observed until 0.02% (4.8 mg/kg/day) of benzo(a)pyrene in decalin alone was applied. The method of application was not specified, sample sizes were small and no decalin solvent controls were included; however decalin is not considered to be carcinogenic. In this same study, subchronic (50 week) dermal application of benzo(a)pyrene dissolved in the cocarcinogens 1-dodecanol or 1-phenyldodecane produced skin tumors in animals exposed to 0.05% benzo(a)pyrene in either solvent. The tumor incidence varied depending on the solvent concentration; however, the latency period was reduced only when 1-dodecanol was the solvent (Bingham and Falk 1969).

Mice receiving 0.001 to 0.01% of benzo(a)pyrene dermally applied to their backs throughout their lifetimes exhibited a dose-response relationship for skin tumors (Wynder and Hoffmann 1959a; Wynder et al. 1957). A dose of 0.001% benzo(a)pyrene produced enhanced skin carcinoma and papilloma incidences (4 and 45%, respectively). In another study conducted by Wynder and Hoffmann (1959b), higher concentrations of benzo(a)pyrene produced an increased incidence (85%) of papillomas and carcinomas. These studies had a number of weaknesses, including no statistical treatment and no solvent control group. Dose quantification is difficult due to the method of application (Wynder and Hoffmann 1959a,b). NMRI mice topically administered 2 μg benzo(a)pyrene throughout their lifetime also developed increased skin tumor incidences (45%) of papillomas and carcinomas (Habs et al. 1984, see Table 2-3). CH3 mice administered a higher dose of 12.5 μg benzo(a)pyrene for 99 weeks exhibited malignant skin tumors (94%) (Warshawsky and Barkley 1987, see Table 2-3). Increased malignant carcinoma incidences in these dermal application studies can be correlated to increasing benzo(a)pyrene concentrations.

In mice, the tumorigenic dose of benzo(a)pyrene is dependent on the strain. For example, Habs et al. (1980) tested 1.7-4.6 μg benzo(a)pyrene (0.016-0.04 mg/kg/day) in order to determine its dose-response relationship as a carcinogen when topically applied to the backs of NMRI mice throughout their lifetimes. A clear-cut dose-response relationship was seen for benzo(a)pyrene and the induction of tumors (most likely including papillomas, since this protocol usually produces only papillomas). The lowest dose at which skin tumors appeared was at 1.7 μg (0.016 mg/kg/day). This strain of NMRI mice also has a high (70%) background incidence rate of systemic tumors, so an evaluation of the effects of benzo(a)pyrene on any organ other than the site of administration was not possible.

Some dermal carcinogenicity experiments described in this section may have underestimated the potency of benzo(a)pyrene because the ability of this compound to induce the enzymes responsible for its metabolic detoxification can reduce its carcinogenicity (Slaga and diGiovanni 1984). Levin et al. (1976) showed that doses of 0.1 nmol benzo(a)pyrene (25 μg) administered to the backs of mice as infrequently as once every 2 weeks elicited an increased (94%) tumor incidence after 60 weeks of treatment (Slaga and diGiovanni 1984; Weibel 1980).

Chrysene. Chrysene has elicited skin tumors following chronic (68-82 weeks) dermal exposure to mice. Topical application of a chrysene solution in n-dodecane/decalin to the skin of mice produced a significant increase in the carcinogenic potency of chrysene compared with that obtained using decalin alone; 26 and 63% of mice exhibited papillomas and carcinomas, respectively at 49 weeks (Horton and Christian 1974). Since only one dose level was employed, no dose-response relationship can be inferred, and no solvent control was included. However, decalin and n-dodecane have been shown in other experiments to be noncarcinogenic in mice (Bingham and Falk 1969). Dermal application of 100 μg chrysene in acetone to the shaved backs of mice resulted in both papillomas and carcinomas (Hecht et al. 1974). The results of the solvent control group were not reported; however, the lack of dermal carcinogenicity of acetone has been well established. An average dose of 1.2 mg/kg/day is the lowest dose of chrysene that has been found to elicit malignant tumors in laboratory animals.

In another chronic study, a higher concentration of chrysene applied dermally to the backs of Swiss mice for a lifetime also resulted in increased papilloma and carcinoma incidences (48 and 42%, respectively) (Wynder and Hoffmann 1959a). Since only one dose was employed, no dose-response information can be inferred from this study.

Dibenz(a,h)anthracene. Dibenz(a,h)anthracene has also demonstrated a dose-response relationship for skin tumors over two orders-of-magnitude dose range following chronic exposure. Swiss mice received concentrations of 0.001-0.1% dibenz(a,h)anthracene applied to their backs throughout their lifetimes and exhibited dose-related papilloma and carcinoma incidences at the site of application at the two lowest doses. The decrease in tumor rate at the highest dose tested probably reflects dibenz(a,h)anthracene's toxicity and the resulting decreased survival observed. The lowest concentration at which dibenz(a,h)anthracene elicited tumors was 0.001% (40% papillomas and 40% carcinomas), which is approximately equal to a dose of 0.029 mg/kg (0.012 mg/kg/day) (Wynder and Hoffmann 1959a). In another chronic dermal study, a dose-related increase in skin carcinoma formation was observed, as well as decreased survival time and tumor latency period (Van Duuren et al. 1967). A dibenz(a,h)anthracene solution applied dermally to Swiss mice produced skin tumors in 80% of the animals (Lijinsky et al. 1965). Dermal application of C3H mice with dibenz(a,h)anthracene for their lifetime also resulted in an increased (90%) incidence of mammary tumors in comparison to the incidence (50%) exhibited by controls (Ranadine and Karande 1963).

Fluoranthene. Chronic dermal application of up to 1% fluoranthene to the backs of mice did not induce skin tumors following a lifetime of application (Hoffmann et al. 1972; Horton and Christian 1974; Wynder and Hoffmann 1959a).

Fluorene. Fluorene has been reported to be negative as a complete carcinogen (dose not specified) (Kennaway 1924).

Indeno(1,2,3-cd)pyrene. Chronic dermal application of indeno(1,2,3-cd)pyrene in dioxane to mice did not produce an increased incidence of skin tumors. However, when acetone was used as the solvent, a dose-related increase in tumor incidence was observed after 9 months (Hoffmann and Wynder 1966). In contrast, chronic topical application of up to 9.2 μg of indeno(1,2,3-cd)pyrene in acetone to the backs of mice for a lifetime resulted in no tumor induction (Habs et al. 1980).

Phenanthrene. Phenanthrene tested negative as a complete carcinogen in two mouse studies that lacked adequate reporting (Kennaway 1924; Roe and Grant 1964).

Pyrene. Mice chronically administered a 10% pyrene solution throughout their lifetimes did not develop skin tumors (Wynder and Hoffmann 1959a). However, prolonged dermal exposure of mice to 0.5% pyrene in decalin:n-dodecane solvent produced a slightly elevated (15%) skin carcinoma incidence; the level of statistical significance was not provided (Horton and Christian 1974).

Initiation-Promotion Studies

Carcinogenesis has been demonstrated to be a multistage process in the cells of certain animal tissues, including skin, lung, liver, and bladder. This process is believed to occur in human tumorigenesis as well. At least two stages are evident in experimentally induced cancers; initiation and promotion. The initiation-promotion model has been generally accepted as being representative of tumor induction. The PAHs have been studied extensively for their ability to act as tumor initiators and/or promoters.

Following is a brief discussion, by chemical, of the results of the initiation-promotion studies performed with 13 of the 15 PAHs discussed in this profile. Only those studies considered adequate and reliable are presented in Table 2-3.

The difficulty inherent in extrapolating initiation-promotion experiments to human exposure precludes their being used as the basis for significant human exposure level development. Since PAHs occur in complex mixtures of chemicals that may include tumor promoters, their activity as initiating agents is noteworthy. Thus, humans dermally exposed to PAHs that are initiating agents concomitantly with other chemicals that may be active as tumor promoters (including other PAHs) found at nearby hazardous waste sites, are likely to be at risk of developing skin cancer.

Anthracene. Anthracene has been found to be inactive as an initiating agent (LaVoie et al. 1983a).

Benz(a)anthracene. Benz(a)anthracene has been observed to be a tumor initiator in a subchronic dermal study. CD-1 mice topically administered 2.5 μmole (0.57 mg) benz(a)anthracene followed by promotion with tetradecanoyl phorbol acetate (TPA) (for 25 weeks) exhibited an increased skin tumor incidence (36%) (Levin et al. 1984, see Table 2-3).

Benzo(a)pyrene. Benzo(a)pyrene is active as a tumor initiator using initiation/promotion protocols. Topical application of a single initiation dose of benzo(a)pyrene to the backs of mice followed by promotion with TPA or croton oil resulted in an enhanced incidence (80-92%) of skin papillomas (Cavalieri et al. 1988b, see Table 2-3; Hoffmann and Wynder 1966). Ten doses of benzo(a)pyrene (0.1 mg/dose) topically applied to the backs of Swiss mice followed by promotion with croton oil (for 20 weeks) resulted in the development of skin tumors (Hoffmann et al. 1972).

Benzo(b)fluoranthene. The potential of benzo(b)fluoranthene to initiate skin tumor formation has also been demonstrated using a standard initiation/promotion protocol with either croton oil or phorbol myristate acetate as a tumor promoter (Amin et al. 1985a; LaVoie et al. 1979, 1982). Dermal applications of initiation doses of benzo(b)fluoranthene (10 to 100 ug) followed by TPA (for 20 weeks) to the backs of CD-1 mice elicited a dose-related skin tumor incidence, predominantly consisting of squamous cell papillomas (LaVoie et al. 1982).

Benzo(k)fluoranthene. Benzo(k)fluoranthene has also been demonstrated to be a tumor initiator in mice, although not as potent as benzo(b)-fluoranthene. Mice receiving initiating doses of benzo(k)fluoranthene (30 to 1000 ug) followed by TPA promotion exhibited a dose-related increase in tumor incidence (LaVoie et al. 1982). A single application of a much larger dose of benzo(k)fluoranthene (11 mg) dermally applied to Swiss mice followed by promoting treatments with croton resin enhanced the incidence of papillomas and carcinomas (90 and 25%, respectively) (Van Duuren et al. 1966). However, benzo(k)fluoranthene alone was not a complete carcinogen as no tumor induction was observed without a promoting agent (Van Duuren et al. 1966). Chronic dermal application of benzo(k)fluoranthene to Swiss mice resulted in no tumors, but skin papillomas were observed in 10% of animals treated with a higher concentration of benzo(k)fluoranthene. Statistical analyses were not performed (Wynder and Hoffmann 1959b). In another study, no significant increase in tumor incidence was observed in NMRI mice painted with up to 9.2 μg benzo(k)fluoranthene for a lifetime; no effect on mortality was noted (Habs et al. 1980).

Benzo(ghi)perylene. Benzo(ghi)perylene has been shown to be inactive as an initiating agent when applied at a total dose of 0.25 mg/animal and negative as a complete carcinogen when a 1% solution was applied thrice weekly for 12 months following dermal exposure (Hoffmann and Wynder 1966; IARC 1983).

Chrysene. Many studies have reported that chrysene is a tumor initiator in classic initiation/promotion bioassays on mouse skin using croton oil or phorbol myristate acetate as promoting agents (Hecht et al. 1974; Van Duuren et al. 1966; Wood et al. 1979). Initiating doses of chrysene followed by promotion with TPA or croton resin induced a dose-related papilloma incidence in mice (Levin et al. 1978; Slaga et al. 1980a; Van Duuren et al. 1966; Wood et al. 1979). Ten daily treatments of chrysene to Swiss mice followed by TPA promotion (for 20 weeks), resulted in an enhanced incidence of papillomas and carcinomas (61%) compared to the chrysene treatment group (Hecht et al. 1974; Scribner 1973).

Dibenz(a,h)anthracene. Dibenz(a,h)anthracene has also demonstrated tumor initiation activity using a standard initiation/promotion protocol (Slaga et al. 1980a). Dibenz(a,h)anthracene has been reported to initiate skin development in a dose-response relationship at doses as low as 0.02 μg administered once (Klein 1960) or 0.028 μg followed by promotion with TPA (for 25 weeks) (Buening et al. 1979a).

Fluoranthene. Fluoranthene did not exhibit initiation activity in Swiss mice topically administered 10 doses of the chemical fluoranthene followed by promotion with croton oil (for 20 weeks) (Hoffmann et al. 1972).

Fluorene. Fluorene has been reported to be negative as a cocarcinogen with 3-methylcholanthrene when applied at a concentration of 0.30% twice weekly for 31 weeks (Riegel et al. 1951). It is also inactive as a tumor initiator when an estimated total dose of 1.0 mg was applied prior to TPA application (LaVoie et al. 1980).

Indeno(1,2,3-cd)pyrene. Indeno(1,2,3-cd)pyrene was observed to have tumor initiating activity at repeated doses of 250 μg (10 applications) followed by promotion with croton oil (Hoffmann and Wynder 1966). A pronounced dose-response relationship has been exhibited in an initiation-promotion bioassay when TPA was employed as the promoting agent, although it was not as potent an initiator as benzo(b)fluoranthene (Rice et al. 1985a, see Table 2-3).

Phenanthrene. Phenanthrene was ineffective as an initiator (LaVoie et al. 1981; Roe 1962; Salaman and Roe 1956; Wood et al. 1979), and also was inactive as a tumor promoter (Roe and Grant 1964). All of these studies were conducted in various mouse strains. CD-1 mice topically administered a single dose of 10 μmol phenanthrene were observed to have a papilloma incidence 2-4 times that of background; however the incidences were not statistically significant in comparison to controls due to the small number of animals tested and the high spontaneous tumor incidence (Wood et al. 1979).

Pyrene. Pyrene has been shown to be inactive as an initiation agent (Badger et al. 1940; Roe and Grant 1964; Salaman and Roe 1956; Scribner 1973; Van Duuren and Goldschmidt 1976).

Mixtures. Co-administration of pyrene and benzo(a)pyrene to the backs of ICR/Ha mice has produced an enhancement of benzo(a)pyrene tumorigenicity (Van Duuren and Goldschmidt 1976; Goldschmidt et al. 1973). There is evidence that benzo(ghi)perylene is a cocarcinogen with benzo(a)pyrene when both are applied simultaneously to the skin of Swiss mice (Van Duuren et al. 1973). Dermal pretreatment with 100 μg pyrene substantially enhanced benzo(a)pyrene tumor initiation in CD-1 mice, while 100 μg fluoranthene produced a marginal enhancement (Slaga et al. 1979).

Chronic dermal exposure of NMRI mice to a tar condensate that contained several PAHs (pyrene, fluoranthene, chrysene, benz(a)anthracene, benzo(a)pyrene, indeno(1,2,3-cd)pyrene, benzo(ghi)perylene) in addition to other compounds produced a carcinogenic effect as evidenced by an increase in the incidence of skin papillomas and carcinomas (Habs et al. 1984). Due to the presence of other compounds in the tar condensate, the carcinogenic effect cannot be definitely attributed to the PAHs present in the mixture.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding the absorption of PAHs in humans following inhalation exposure. However, absorption of PAHs following inhalation can be inferred from the presence of urinary metabolites of PAHs in workers exposed to these compounds in an aluminum plant (Becher and Bjorseth 1983). The high concentration of PAHs in the occupational setting did not correspond to the amount of PAHs deposited, metabolized and excreted in the urine in this study. The authors suggested that PAHs adsorbed to airborne particulate matter may not be bioavailable, and that the dose-uptake relationship may not be linear over the entire PAH concentration range.

Many studies were available in animals regarding the absorption of benzo(a)pyrene following inhalation exposure. In one study, Sun et al. (1982) administered [^{3}H]-benzo(a)pyrene (0.6 μg/L) adsorbed on Ga_2O_3 particles as an aerosol to rats. A control study was conducted without the Ga_2O_3 particles at a concentration of 1 μg/L. After 30 minutes of exposure, the fraction of the total amount of aerosol particles deposited in the lung was approximately 20% for Ga_2O_3 and approximately 10% for the pure hydrocarbon aerosol. The excretion of hydrocarbon was monitored for over two weeks at which time nearly all the radioactivity was recovered, indicating complete absorption of the initially instilled hydrocarbon. Significant differences in the clearance of Ga_2O_3-adsorbed and pure benzo(a)pyrene suggested that a substantial amount of benzo(a)pyrene coated on Ga_2O_3 particles was removed from the lungs by mucociliary clearance and subsequent ingestion. The pure benzo(a)pyrene particles retained by the lungs were removed by absorption into the blood stream. The association of benzo(a)pyrene with the particles increased the retention of benzo(a)pyrene in the lung and increased the relative amount of benzo(a)pyrene that was cleared by mucociliary action and subsequently ingested. Hence, there was an increase in the absorption of benzo(a)pyrene in the alimentary tract thus increasing the dose of benzo(a)pyrene and its metabolites to the stomach, liver and kidneys relative to pure benzo(a)pyrene.

The size of the particles on which benzo(a)pyrene is adsorbed affects the pulmonary absorption and elimination of this chemical. For example, the elimination of benzo(a)pyrene from the lungs was studied following intratrachael administration of pure benzo(a)pyrene crystals and benzo(a)pyrene-coated on carbon particles in two size ranges (0.1-1.0 μm and 15-30 μm) (Cresia et al. 1976). Whereas 50% of the pure benzo(a)pyrene crystals was eliminated from the lungs within 1.5 hours and 95% within 24 hours, the benzo(a)pyrene adsorbed to the small carbon particles took 36 hours to clear 50% of the initial dose. Elution was even slower with the larger particle size (approximately 4-5 days). These results indicate that the bioavailability of benzo(a)pyrene is altered by the particle size of the carrier.

Intratracheal administration of [^{3}H]-benzo(a)pyrene (0.001 mg/kg) to rats resulted in its rapid absorption. Radioactivity in the liver reached a maximum of 21% of the dose within 10 minutes of instillation (Weyand and Bevan 1986, 1988). Presence of radioactivity in other tissues and the bile was also indicative of its absorption. Similar results were also seen in guinea pigs and hamsters following intratracheal exposure (Weyand and Bevan 1986, 1987b, 1988).

Nasal instillation of [^{3}H]-benzo(a)pyrene (0.13 mg/kg) to hamsters resulted in the metabolism of [^{3}H]-benzo(a)pyrene in the nasal cavity. A large fraction of the metabolites was recovered from the epithelial surface, indicating that benzo(a)pyrene was first absorbed in the mucosa, metabolized, and returned to the mucus (Dahl et al. 1985).

Monkeys and dogs received nasal instillation of [^{14}C]-benzo(a)pyrene at doses of 0.16-0.21 mg/kg. Radiolabeled metabolites were detected in the nasal cavity, but little or no activity was detected in the blood and excreta of either species during the 48 hours after exposure. These results indicate that there was either little or very slow direct transfer of benzo(a)pyrene or its metabolites into the blood (Petridou-Fischer et al. 1988).

2.3.1.2 Oral Exposure

Indirect evidence suggests that benzo(a)pyrene may not be readily absorbed following oral exposure in humans. The concentration of benzo(a)pyrene in human feces was studied after eight volunteers ingested broiled meat that contained approximately 9 μg of benzo(a)pyrene (Hecht et al. 1979). Less than 0.1 μg/person (i.e., below the detection limit) of benzo(a)pyrene was detected in the feces of these individuals, which is similar to what was seen following consumption of control meat that contained undetectable amounts of benzo(a)pyrene by these same volunteers. The gastrointestinal absorption of benzo(a)pyrene was also studied in the rat. [^{14}C]-benzo(a)pyrene was administered to rats by gavage (0.04 μmol, 0.4 μmol, 4.0 μmol). These same authors also fed rats charbroiled meat that contained 52.7 μg/kg benzo(a)pyrene. Total excretion of radioactivity in the feces averaged 74%-79% and 85% at 48 and 168 hours, respectively, following gavage administration. Only 1%-3% of the administered dose was excreted in the urine. The amount of parent compound excreted decreased as the dose increased Unchanged benzo(a)pyrene was detected in the feces of those rats that ingested charbroiled meat at at level of 0.06 μg/kg (Hecht et al. 1979). It was suggested by the authors that the lower excretion of benzo(a)pyrene in the feces by humans as compared to rats may be due to differences in the metabolism of benzo(a)pyrene by the liver or fecal microflora or other undetermined factors. Radiolabeled benzo(a)pyrene was absorbed in Sprague-Dawley rats following oral administration as evidenced by the detection of radioactivity in liver, lung and kidney fractions (Yamazaki et al. 1987). These results indicate that benzo(a)pyrene is absorbed following oral administration in the rat.

Oral absorption of benz(a)anthracene in rats was rapid and efficient. Levels of benz(a)anthracene in the blood, liver, and brain reached a maximum within 1-2 hours after administration (Modica et al. 1982).

Intestinal absorption of chrysene could not be quantified, but its extent of absorption in rats was dependent on the oral dose of chrysene and the vehicle of administration. Approximately 25%-41% of the chrysene dose

(22.8 mg/kg in olive oil) was recovered in the feces within 72 hours after administration (Modica et al. 1982). Chang (1943) reported an excretion of 79% of the chrysene dose in the feces following dietary (500 mg/kg) and gavage (200 mg/kg) administration.

Administration of dibenz(a,h)anthracene in the diet (250 mg) or by stomach tube (200 mg) resulted in greater than 90% of the dose being excreted in the feces of white rats (Chang 1943). As with chrysene, absorption of dibenz(a,h)anthracene could not be quantified.

The intestinal absorption of PAHs is highly dependent on the presence of bile in the stomach (Rahman et al. 1986). To study the role of bile in the intestinal absorption of PAHs, conscious rats with bile duct and duodenal catheters were given isotopically labeled benzo(a)pyrene, phenanthrene, anthracene, 2,6-dimethylnaphthalene (DMN), and 7,12-dimethylbenz(a)anthracene (DMBA) in corn oil with or without exogenous bile. The efficiency of PAH absorption was estimated from the cumulative recovery of radioactivity in the bile and urine over 24 hours. The efficiencies of absorption without bile (as a percentage of absorption with bile) were: benzo(a)pyrene, 22.9%; phenanthrene, 96.7%; anthracene 70.8%; DMN, 91.6%; DMBA 43.4%. Absorption of the four- or five-membered rings (DMBA and benzo(a)pyrene) was strongly dependent on the presence of bile in the intestinal lumen. The absorption of the tricyclic PAHs (phenanthrene and anthracene) differed with respect to their dependency on bile for efficient absorption. This difference correlated with a difference in water solubility, with anthracene being 18 times less water-soluble than phenanthrene. Those products with low water solubility are dependent on the creation of an intermediate phase of the products of lipolysis and bile salts. These reactions occur during the normal process of lipid digestion and absorption in the intestine.

In general, PAH absorption following the ingestion of contaminated food or drinking water depends on the compound's vehicle of administration. The extent of PAH absorption is enhanced when they are solubilized in a vehicle that is readily absorbed, such as certain oils (e.g., corn oil).

2.3.1.3 Dermal Exposure

Application of 2% crude coal tar to the skin of humans for 8-hour periods on 2 consecutive days yielded evidence of PAH absorption (Storer et al. 1984). Phenanthrene, anthracene, pyrene, and fluoranthene were detected in the blood, but benzo(a)pyrene was not detected; thus absorption of PAHs in crude coal tar was variable. This variability was attributed to differences in percutaneous absorption, rapid tissue deposition after absorption, or metabolic conjugation with rapid urine excretion. An *in vitro* study using human skin revealed that the extent of permeation after 24 hours was established as 3% of an applied dose of [^{14}C]-benzo(a)pyrene (10 $\mu g/cm^2$) (Kao et al. 1985).

Percutaneous absorption of [^{14}C]-benzo(a)pyrene in mice was evident after monitoring the appearance of radioactivity in excreta and analyzing the residual activity at the site of application. Disappearance of the applied dose from the application site was 6 and 40% at 1 and 24 hours following administration, respectively. Seven days after exposure, 93% of the radioactivity was recovered in the feces (Sanders et al. 1986).

The percutaneous absorption of [^{14}C]-anthracene (9.3 μg/cm^2) was estimated in rats by measuring radioactivity in urine, feces, and tissues over a six-day period (Yang et al. 1986). Approximately 52.3% of the dose was absorbed. Over time, the permeation of anthracene significantly decreased suggesting that anthracene was dermally absorbed in a dose-dependent manner. Diffusion of anthracene through the skin (stratum corneum) depended on the amount of anthracene on the skin's surface.

Metabolism of chrysene at relatively high rates in mouse skin provides evidence of its dermal uptake (Hodgson 1983; Weston et al. 1985). Dibenz[a,h]anthracene was also dermally absorbed, but not to the extent seen with benzo(a)pyrene. Sanders et al. (1986) applied [^{14}C]-dibenz(a,h)-anthracene (5.4, 56, 515 μg/cm^2) and [^{14}C]-benzo(a)pyrene (1.25-125 μg/cm^2) to the nuchal area on the shaved backs of mice. The [^{14}C]-activity of the skin at the application site, in excreta, and in exhaled air were monitored. At 24 hours after the maximum dose of dibenz(a,h)anthracene was applied, 67.2% of the activity was recovered from the application site, 25.4% from body tissues, and 7.4% from excreta. Under similar conditions with benzo(a)pyrene, 17.4, 36.6, and 46.8% of the activity was recovered from the application site, tissue, and excreta, respectively. The amount absorbed did not increase linearly with dose due to an apparent saturation of the uptake process. The difference in dermal uptake may be attributable to the lower rate of dibenz(a,h)anthracene metabolism relative to benzo(a)pyrene (Sanders et al. 1986).

Monitoring the removal of compounds from the epidermis is indicative of measuring the compound's dermal absorption. The disappearance of radiolabeled benzo(a)pyrene and its metabolites from the epidermis was monophasic, following first order kinetics with a half-life of approximately 2 hours (Melikian et al. 1987). Recovery of the radiolabel was 99%-100% throughout the period of the experiment (8 hours), indicating that volatilization of benzo(a)pyrene from the skin was not a confounding factor (Melikian et al. 1987). In contrast, removal of one of its metabolites, 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene (anti-BPDE), from the epidermis was biphasic. The second, slower phase of removal suggested that the stratum corneum, the outermost layer of skin which consists of several layers of inactive, keratinized cells surrounded by extracellular lipids, may act as a reservoir that can retain and slowly release topically applied lipophilic substances such as benzo(a)pyrene but is penetrated rapidly by more polar compounds such as anti-BPDE.

In conclusion, PAHs are absorbed through the skin of both humans and animals. Therefore, skin contact with soil and water contaminated with PAHs at hazardous waste sites can result in exposure to these compounds. Systemic absorption of PAHs from the skin is variable among these compounds.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding the distribution of PAHs in humans following inhalation exposure. Results from a study in rats in which [^{3}H]-benzo(a)pyrene was intratracheally administered demonstrated that the highest fractions were distributed to the lung, liver, kidney, gastrointestinal tract, and carcass (Weyand and Bevan 1986, 1987a, 1988). The concentration of benzo(a)pyrene and its metabolites in the intestines increased with time, suggesting the occurrence of biliary excretion and enterohepatic recirculation. Tissue distribution of radioactivity was qualitatively similar in guinea pigs and hamsters (Weyand and Bevan 1987b). Mice that received benzo(a)pyrene intratracheally also experienced a similar tissue distribution, but Schnizlein et al. (1987) noted that as the lung burden of benzo(a)pyrene diminished, radioactivity continued to increase in the lung-associated lymph nodes for six days. This accumulation may eventually affect humoral immunity.

The distribution patterns of benzo(a)pyrene following aerosol exposure with or without Ga_2O_3 were similar. Maximum levels were achieved in the liver, esophagus, small intestine, and blood at 30 minutes following exposure. At 12 hours, maximum levels were seen in the lower gastrointestinal tract. However, significant differences in the levels of benzo(a)pyrene delivered to the different tissues did exist. Higher tissue levels of hydrocarbon resulted from absorption of benzo(a)pyrene-Ga_2O_3 particles. Inhaled benzo(a)pyrene adsorbed on insoluble particles was cleared predominantly by mucociliary transport and ingestion. This latter mechanism of absorption led to the increased levels of benzo(a)pyrene in the liver and kidneys. Furthermore, benzo(a)pyrene that was absorbed via the intestinal tract was distributed in a pattern analogous to that seen with inhaled benzo(a)pyrene particles (Sun et al. 1982).

2.3.2.2 Oral Exposure

No studies were located regarding the distribution of PAHs in humans following oral exposure. However, [^{3}H]-benzo(a)pyrene orally administered to rats (0.004 mg/kg) primarily distributed to the protein fractions of the liver, lung, and kidney. The radioactivity in the protein fractions of these tissues increased gradually over time. In contrast, the radioactivity in the lipid fractions of these tissues accounted for 70% of the administered dose at 3 hours, but decreased rapidly with time. The nucleic acid fraction maintained approximately 10% of the total radioactivity throughout the experiment. The increase in protein binding several hours after administration facilitated the persistence of benzo(a)pyrene metabolites. Also, the proteins in lung and kidney may contribute to the cytotoxicity, mutagenicity or carcinogenicity of benzo(a)pyrene and its metabolites since these organs have low metabolic activity while the liver has a high detoxification potential and can expedite the excretion of these toxic products (Yamazaki et al. 1987).

Orally absorbed benz(a)anthracene and chrysene were rapidly and widely distributed in the rat (Bartosek et al. 1984). Maximum concentrations in perfused tissues, like the liver, blood, and brain, were achieved within 1-2 hours after administration. Maximum levels in lesser perfused tissues, like adipose and mammary tissue, were reached in 3-4 hours. At 72 hours after oral administration, benz(a)anthracene had the greatest affinity for adipose, sequentially followed by mammary, brain, liver, and blood (Bartosek et al. 1984).

Orally absorbed dibenz(a,h)anthracene was also widely distributed to several tissues. However, maximum tissue concentrations were not reached until 10 hours after administration. Highest tissue concentrations were in the liver and kidneys, followed by adrenal glands, ovaries, blood, and fat. Soon after administration, large quantities of dibenz(a,h)anthracene were found in the liver and kidneys. The elimination rate from these organs was rapid. At 3-4 days after administration, dibenz(a,h)anthracene was distributed only in the adrenal glands, ovaries and fat (Daniel et al. 1967).

The permeability of the placenta to DMBA, benzo(a)pyrene, and 3-methylcholanthrene (MC) was studied by Shendrikova and Aleksandrov (1974). Pregnant rats received the PAH orally in sunflower oil at a dose of 200 mg/kg on the 21st day of pregnancy. Within 30 minutes after administration of DMBA, trace amount of the compound could be detected in the fetus. Maximum levels (1.53-1.6 μg/g) were reached between 2-3 hours after administration. Only trace amounts were detected in the fetus at five hours after administration. Concentration profiles in the liver and placenta were similar to those seen in the fetus. The permeability of benzo(a)pyrene through the placenta to the fetus (2.77 μg/g) was considerably greater than with DMBA. MC was only present in trace amounts. Concentration differences in the fetus among the various PAHs appeared to be highly dependent on the gastrointestinal absorption of the compound. The difference in fetal concentration of the PAHs did not reflect their ability to permeate the placenta.

2.3.2.3 Dermal Exposure

No studies were located regarding the distribution of PAHs in humans following dermal exposure. Evidence regarding its distribution in animals following dermal exposure is limited. Although PAHs can readily penetrate the skin, very little is distributed to tissues. Only 1.3% of an applied dose of $[^{14}C]$-anthracene (9.3 $\mu g/cm^2$) was detected in tissues of rats at six days after administration (Yang et al. 1986). Animal studies with a PAH not included in this profile (dimethylbenzanthracene) indicate that absorption and distribution of PAHs through the skin is not extensive.

2.3.3 Metabolism

The lipophilicity of PAHs enables them to readily penetrate cellular membranes and remain in the body indefinitely. However, the metabolism of PAHs alters these chemicals both chemically and structurally, rendering them more water-soluble and more excretable. Metabolism of PAHs occurs in all tissues. The metabolic process involves several possible pathways with varying degrees of enzyme activities. The activities and affinities of the enzymes in a given tissue determine which metabolic route will prevail.

PAH metabolism has been studied extensively in vitro and in vivo. The most commonly used system is the rat liver microsomal fraction, although other species are used. Cells and cultured tissues from human and other animals have also significantly contributed to the elucidation of the PAH metabolic scheme.

The structural similarity of PAHs contributes to the similarities that exist in their biotransformation. Benzo(a)pyrene metabolism has been extensively reviewed and will be used as a model for PAH metabolism. In the many microsomal, cell, and cultured tissue preparations that have been examined, the metabolic profiles are qualitatively similar. However, there are differences in the relative levels and rates of formation of specific metabolites among tissues and cell preparations used from various animal species and strains. These differences are susceptible to change as a result of pretreatment of the animals with either inducers or inhibitors of particular enzymes. Furthermore, it is known that the metabolism of alternant PAHs (such as benzo(a)pyrene, benz(a)anthracene, chrysene, and dibenz(a,h)anthracene) differs from non-alternant PAHs (such as benzo(b)fluoranthene, benzo(k)fluoranthene, and indeno(1,2,3-cd)pyrene) (see Section 2.2). Therefore, the metabolism of benzo(b)fluoranthene will also be discussed as a model for non-alternant PAH metabolism.

The metabolism of benzo(a)pyrene is summarized in Figure 2-3. Benzo(a)pyrene is metabolized initially by the microsomal P-450 systems to several arene oxides. Once formed, these arene oxides may rearrange spontaneously to phenols, undergo hydration to the corresponding trans-dihydrodiols in a reaction catalyzed by microsomal epoxide hydrolase, or react covalently with glutathione, either spontaneously or in a reaction catalyzed by cytosolic glutathione-S-transferases. Phenols may also be formed by the P-450 system by direct oxygen insertion, although unequivocal proof for this mechanism is lacking. 6-Hydroxybenzo(a)pyrene is further oxidized either spontaneously or metabolically to the 1,6-, 3,6-, or 6,12-quinones. This phenol is also a presumed intermediate in the oxidation of benzo(a)pyrene to the three quinones catalyzed by prostaglandin endoperoxide synthetase (Panthanickal and Marnett 1981). Evidence exists for the further oxidative

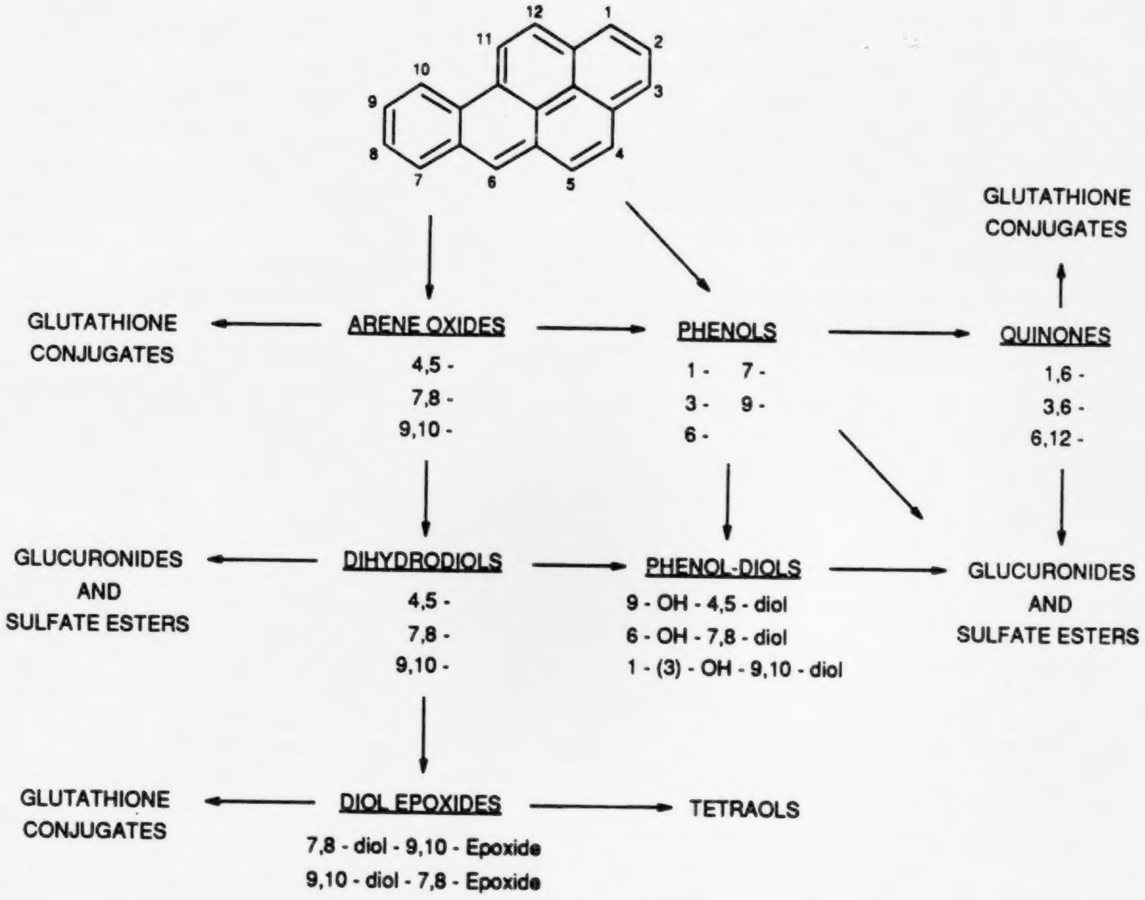

12
1
11
2
10
3
9
8
4
7
6
5
GLUTATHIONE CONJUGATES
GLUTATHIONE CONJUGATES
ARENE OXIDES
4,5 -
7,8 -
9,10 -
PHENOLS
1 - 7 -
3 - 9 -
6 -
QUINONES
1,6 -
3,6 -
6,12 -
GLUCURONIDES AND SULFATE ESTERS
DIHYDRODIOLS
4,5 -
7,8 -
9,10 -
PHENOL-DIOLS
9 - OH - 4,5 - diol
6 - OH - 7,8 - diol
1 - (3) - OH - 9,10 - diol
GLUCURONIDES AND SULFATE ESTERS
GLUTATHIONE CONJUGATES
DIOL EPOXIDES
7,8 - diol - 9,10 - Epoxide
9,10 - diol - 7,8 - Epoxide
TETRAOLS

FIGURE 2-3. Proposed Metabolic Scheme for Benzo(a)pyrene

metabolism to two additional phenols. 3-Hydroxybenzo(a)pyrene is metabolized to the 3,6-quinone and 9-OH-benzo(a)pyrene is oxidized to the K-region 4,5-oxide, which is hydrated to the corresponding 4,5-dihydrodiol. The phenols, quinones, and dihydrodiols can all be conjugated to glucuronides and sulfate esters; the quinones also form glutathione conjugates (IARC 1983).

In addition to being conjugated, the dihydrodiols undergo further oxidative metabolism. The cytochrome P-450 system metabolizes benzo(a)pyrene-4,5-dihydrodiol to a number of uncharacterized metabolites, while the 9,10-dihydrodiol is metabolized predominantly to its 1- and/or 3-phenol derivative with only minor quantities of a 9,10-dihydrodiol-7,8-epoxide being formed. In contrast to a 9,10-dihydrodiol, benzo(a)pyrene-7,8-dihydrodiol is metabolized to a 7,8-dihydrodiol-9,10-epoxide, and phenol-diol formation is a relatively minor pathway. The diol epoxides can be conjugated with glutathione either spontaneously or by a glutathione-S-transferase catalyzed reaction. They may also hydrolyze spontaneously to tetraols.

The route by which PAHs and other xenobiotics enter the body may determine their fate and organ specificity. For example, an inhaled compound may bypass the first-pass effect of the liver and reach peripheral tissues in concentrations higher than one would see after oral exposures. Enzyme activities among tissues are variable and may subsequently alter the degree of bioavailability.

Benzo(a)pyrene was metabolized by human bronchial epithelial and lung tissue *in vitro* to the 9,10-dihydrodiol, 7,8-dihydrodiol, and small quantities of the 4,5-dihydrodiol and 3-hydroxybenzo(a)pyrene, all which are extractable into ethyl acetate (Autrup et al. 1978; Cohen et al. 1976; Kiefer et al. 1988). These metabolites also conjugated with glutathione and sulfates, but none conjugated with glucuronide. The rate of formation of the dihydrodiols was greater in the bronchial epithelium than in the lung (Autrup et al. 1978; Cohen et al. 1976). This may render some areas of the respiratory tract more sensitive to the effects of carcinogens. One principal difference seen in human lung was the generation of a major ethyl acetate-soluble metabolite that was identified as the sulfate conjugate of 3-hydroxybenzo(a)pyrene, benzo(a)pyrene-3-yl-hydrogen sulfate. This sulfate is very lipid soluble, thus it would not be readily excreted in the urine. Its molecular weight of 349 falls below the threshold for biliary excretion of 500 in humans. Hence, its physicochemical properties suggest that it may be retained in the body for a long period of time (Cohen et al. 1976).

Intratracheal instillation of benzo(a)pyrene to rats resulted in quinones constituting the highest concentration of metabolites in the lung and the liver within 5 minutes after instillation (Weyand and Bevan 1986, 1988). An *in vitro* study with rat lung demonstrated that the lung tissue has a high capacity to metabolize benzo(a)pyrene at the sixth position to quinones and subsequently to water-soluble products. Ozone exposure resulted in an increase in metabolism to all benzo(a)pyrene metabolites with the greatest increase observed in the formation of products involving sixth position metabolism of benzo(a)pyrene. The proposed retention of quinones following ozone exposure might lead to cytotoxicity associated with superoxide-anion generation by quinone-quinol redox-cycling. However, the high levels of benzo(a)pyrene used in this in vitro study may not be applicable in vivo. Metabolism of benzo(a)pyrene at the sixth position was higher at a lower dose than at the higher dose. Therefore, quinone production and detoxification may represent a major pathway of lung PAH detoxification in vivo (Basett et al. 1988).

Approximately 50% of the benzo(a)pyrene that was intratracheally instilled in hamsters was metabolized in the nose. The metabolite produced in the hamster nose included tetrols, 9,10-dihydrodiols, 4,5-dihydrodiols, 7,8-dihydrodiols, quinones, 3-phenols, and 9-phenols. A prevalence of quinone production was not seen in hamsters as it was in rats (Dahl et al. 1985). In vitro metabolism of benzo(a)pyrene in the ethmoid turbinates of dogs resulted in a prevalence of phenols. However, small quantities of quinones and dihydrodiols were also identified (Bond et al. 1988).

Rat lung microsomes facilitated the transfer of small amounts of benzo(a)pyrene from diesel particles, but only a small fraction of the amount transferred was metabolized. The ability to transfer benzo(a)pyrene was related to the lipid content of the microsomal fraction. Microsomes are able to enhance the slow transfer of a small amount of benzo(a)pyrene from diesel particles in a form that can be metabolized. Free benzo(a)pyrene was principally and extensively metabolized to the 9,10-dihydrodiol (Leung et al. 1988).

A human hepatoma cell line has high benzo(a)pyrene-metabolizing activity and converts benzo(a)pyrene to metabolites. When [^{3}H]-benzo(a)pyrene was added to the incubate, a large fraction of the radioactivity was not extractable into chloroform. That which was extractable contained 9,10-dihydrodiols, 7,8-dihydrodiols, quinones, 3-hydroxybenzo(a)pyrene and the parent compound. The cell lysate also consisted of the same metabolites, but the proportions of 3-hydroxybenzo(a)pyrene and the parent compound were much higher than in the medium. Conversely, the proportion of water-soluble metabolites in the cell lysate was lower than in the medium. Treatment of the medium and cell lysate with beta-glucuronidase converted only 5-7% of the water-soluble metabolites to chloroform-extractable material. Aryl sulfatase had no effect on radioactivity. These results suggested that this human liver cell line does not extensively utilize the phenol detoxification pathway (Diamond et al. 1980).

Metabolism of benzo(a)pyrene in the primary culture of human hepatocytes primarily resulted in the formation of 3-hydroxybenzo(a)pyrene, 4,5-dihydrodiol, 9,10-dihydrodiol, and 7,8-dihydrodiol. As the dose of benzo(a)pyrene increased, the amount of metabolites increased linearly. Binding to DNA was associated with the amount of unconjugated 7,8-dihydrodiol.

DNA binding was linear up to a benzo(a)pyrene concentration of 100 μM. At this concentration, binding increased 64 to 844 times over the extent of binding at 10 μM. As the concentration of benzo(a)pyrene increased, the ratio of dihydrodiol/phenolic metabolites also increased. Although the capacity to form dihydrodiols was not saturated at 100 μM benzo(a)pyrene, there was a change in the relative proportion of the dihydrodiol metabolites formed as the dose of benzo(a)pyrene increased. As benzo(a)pyrene concentration increased, the 9,10-dihydrodiol was the more prevalent metabolite, but levels of 7,8-dihydrodiol also increased (Monteith et al. 1987).

Epoxide hydrolase is a microsomal enzyme that converts alkene and arene oxides to dihydrodiols. Appreciable enzyme activity was observed in human livers. Comparison of epoxide hydrolase activities with various substrates revealed that the human liver has a single epoxide hydrolase with broad substrate specificity (Kapitulnik et al. 1977). Epoxide hydrolase activity is also present in other tissues and increases the likelihood for carcinogenic effects in these organs. Ethyl acetate extracts of human and rat bladder cultures contained 9,10-dihydrodiol, 7,8-dihydrodiol, and 3-hydroxy-benzo(a)pyrene. Covalent binding of [^{3}H]-benzo(a)pyrene with DNA occurring in both human and rat bladder cultures suggested that benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide is generated. The urothelium of the bladder clearly has the ability to generate the ultimate carcinogen (Moore et al. 1982).

Hepatic microsomes from rats induced with 3-methylcholanthrene convert benzo(a)pyrene to benzo(a)pyrene-7,8-dihydrodiol-9,10-oxide (BPDE) ten times faster than untreated microsomes. The rate limiting step in BPDE formation is the competition for P-450 between benzo(a)pyrene and the 7,8-dihydrodiol. Formation of BPDE is directly correlated with the 3-methylcholanthrene inducible form of P-450 (Keller et al. 1987). Formation of the proximate carcinogen, 7,8-dihydrodiol, is stereoselective. Rabbit hepatic microsomes generated more of the 7R,8R enantiomer with an optical purity of greater than 90% (Hall and Grover 1987). The major stereoisomer formed by rat liver microsomes is (+)-diol-epoxide-2 (Jerina et al. 1976, 1980). This metabolite is highly tumorigenic (Levin et al. 1982) and gives rise to the major adduct formed upon reaction with DNA. The adduct is a diol epoxide-deoxyguanosine formed by alkylation at the exocyclic nitrogen (N-2) of deoxyguanosine. This diol epoxide-deoxyguanosine has been isolated from several animal species (Autrup and Seremet 1986; Horton et al. 1985) and human tissue preparations (Harris et al. 1979).

Several xenobiotics can induce enzymes to influence the rat liver microsomal metabolite profiles of various PAHs. For example, aryl hydrocarbon hydroxylase (AHH), an enzyme believed to be responsible for the metabolism of benzo(a)pyrene and other PAHs, is subject to induction by PAHs. In studying benz(a)anthracene metabolism, some xenobiotics were found to be weak or moderate inducers, but even less efficient ones altered the benz(a)anthracene profile significantly. Thiophenes equally enhanced oxidation at the 5,6- and the 8,9-positions. Benzacridines favored K-region oxidation (5,6-oxidation)

(Jacob et al. 1983). Indeno[1,2,3-c,d]pyrene stimulated the bay region oxidation (3,4-oxidation) of benz(a)anthracene (Jacob et al. 1985). Similar xenobiotic effects were observed with chrysene as a substrate (Jacob et al. 1987). While some enzyme activities are being enhanced, alternate enzymatic pathways may be suppressed (Jacob et al. 1983).

Rat liver microsomes also catalyzed benzo(a)pyrene metabolism in cumene hydroperoxide (CHP)-dependent reactions which ultimately produced 3-hydroxybenzo(a)pyrene and benzo(a)pyrene-quinones. At low CHP concentrations, 3-hydroxybenzo(a)pyrene was the major metabolite. As CHP concentrations increased, levels of quinones increased and levels of 3-hydroxybenzo(a)pyrene decreased. This effect of varying CHP levels was reversed by preincubating with pyrene. Pyrene inhibited quinone production and increased 3-hydroxybenzo(a)pyrene production. Pretreatment with other PAHs like naphthalene, phenanthrene, and benz(a)anthracene nonspecifically inhibited the overall metabolism. The binding of benzo(a)pyrene to microsomal proteins correlated with quinone formation. This suggested that a reactive intermediate was a common precursor. The effects of pyrene on benzo(a)pyrene metabolism indicated that two distinct binding sites were responsible for the formation of 3-hydroxybenzo(a)pyrene and benzo(a)pyrene-quinone (Cavalieri et al. 1987).

Rat mammary epithelial cells (RMEC) have been shown to activate PAHs. Cytochrome-P-450 in RMEC is responsible for the monooxygenation of DMBA. Prior exposure of cultured cells to benz(a)anthracene induced DMBA metabolism. The metabolite profile following benz(a)anthracene-induction was significantly different from the profile obtained with purified P-450c, the predominant PAH-inducible enzyme in rat liver. The bay region 3,4-dihydrodiol, which was not formed with P-450c, was clearly detectable in RMEC. Low epoxide hydrolase activity in the benz(a)anthracene-induced RMEC limited the formation of all other DMBA dihydrodiols. The DMBA monooxygenase activity of benz(a)-anthracene-induced RMEC was inhibited by alpha-napthaflavone. The study concluded that DMBA metabolism by RMEC depended on the induction of P-450c and at least one additional form of P-450 that is sensitive to alpha-napthaflavone (Christou et al. 1987).

As expected by results from other studies, the perfused rat lung can release high quantities of benzo(a)pyrene metabolites and conjugates into the perfusate. Addition of a liver to this perfusion system reduces the concentration of parent compound and free metabolites to less than 20% of that seen in the liver's absence. The liver provides a protective effect on the lung to inhibit covalent binding of benzo(a)pyrene metabolites to pulmonary macromolecules (Molliere et al. 1987).

Fiume et al. (1983) explored the effects of various factors that can modify the hepatic clearance of PAHs. Specifically, the authors used benz(a)anthracene and chrysene. The hepatic clearance and rate constants of these PAHs were significantly reduced in the perfused livers of fasted rats relative to those of fed rats. This reduction was attributed to a decrease in aryl hydrocarbon hydroxylase activity. Fasting also accelerated the depletion of cytochrome P-450 and other microsomal enzymes. In contrast, pretreatment of the rats with these PAHs resulted in increased clearance of both hydrocarbons from the perfusion medium when compared to control rats.

Fiume et al. (1983) also noted that the livers of male rats demonstrated a significantly higher hepatic clearance of benz(a)anthracene than female rats, perhaps suggesting a sexual difference with aryl hydrocarbon hydroxylase activity. Similar findings regarding sexual differences in the metabolism of chrysene by rat livers were also reported by Jacob et al. (1985, 1987). Furthermore, Fiume et al. (1983) demonstrated that age can play a role in PAH metabolism. The hepatic clearance of PAHs in older rats (2 years) was significantly less than the hepatic clearance in younger rats (8 weeks).

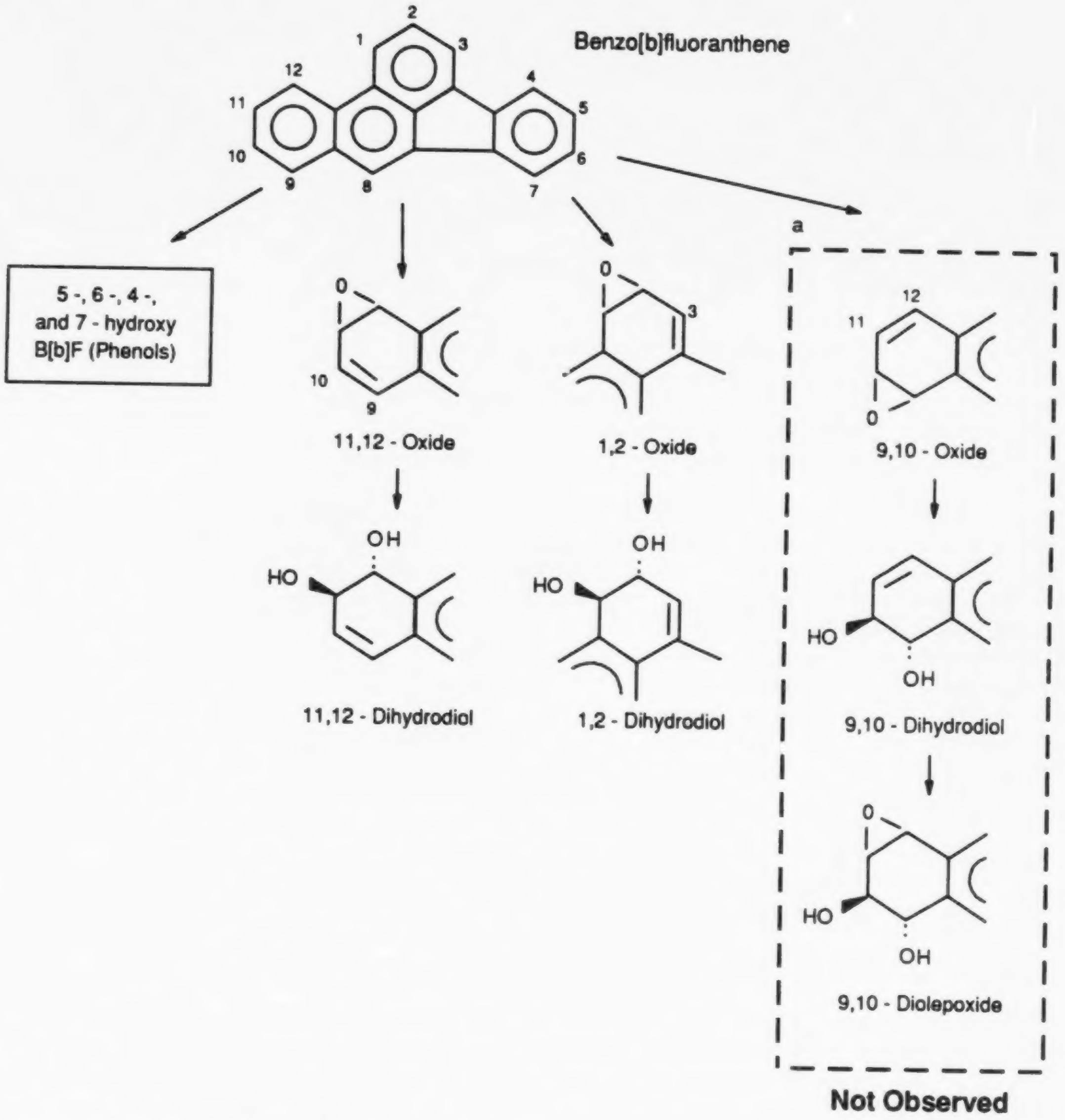
A proposed metabolic scheme for the metabolism of the non-alternant PAH, benzo(b)fluoranthene is presented in Figure 2-4. Using rat liver microsomes, the major metabolites of benzo(b)fluoranthene have been identified as 5- and 6-hydroxybenzo(b)fluoranthene and 4- or 7-hydroxybenzo(b)fluoranthene. The predominant diol formed was trans-11,12-dihydry-11,12-dihydroxybenzo(b)-fluoranthene. No evidence was obtained to indicate the formation of trans-9,10-dihydro-9,10-dihydroxybenzo(b)fluoranthene or 7b,8-dihydro-7b,8-dihydroxybenzo(b)fluoranthene (Amin et al. 1982, 1985b). The former metabolite would be the precursor to a bay-region diol epoxide, believed to be the reactive carcinogenic form of the alternant PAHs. Therefore, it is possible that the reactive intermediates associated with the tumorigenic effects of benzo(b)fluoranthene and other non-alternant PAHs are not bay-region diol epoxides (Amin et al. 1982, 1985b).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located in humans regarding the excretion of PAHs following inhalation exposure. However, studies were available monitoring the excretion of benzo(a)pyrene in animals. A single intratracheal instillation of [^{3}H]-benzo(a)pyrene (2.5 mg/kg) cleared rapidly from the lungs of a mouse with a half life of approximately 8 hours. At 24 hours after instillation, approximately 85% of the burden was cleared from the lung (Schnizlein et al. 1987). Weyand and Bevan (1986) also found the elimination of benzo(a)pyrene from the rat lung to be very rapid. Elimination of activity from the lungs was biphasic with rapid and slow phase half lives of 5 and 16 minutes, respectively. Within 5 minutes, 40% of the dose was cleared from the lung while greater than 94% of the dose was cleared at 360 minutes (Weyand and Bevan 1988).

Only a small percentage of instilled radioactivity (<10%) was excreted in the urine and feces of dogs and monkeys 48 hours after intratracheal


Benzo[b]fluoranthene
1
2
3
4
5
6
7
8
9
10
11
12
a
5 -, 6 -, 4 -, and 7 - hydroxy B[b]F (Phenols)
11,12 - Oxide
11,12 - Dihydrodiol
1,2 - Oxide
1,2 - Dihydrodiol
9,10 - Oxide
9,10 - Dihydrodiol
9,10 - Diolepoxide
O
OH
HO
Not Observed

[a] The box contains the metabolic pathway to the bay-region diol epoxide normally thought to be the active metabolite for PAHs. It is not observed in the metabolism of benzo(b)fluoranthene.

FIGURE 2-4. Proposed Metabolic Scheme for Benzo(b)fluoranthene

administration of [^{3}H]-benzo(a)pyrene (Petridou-Fischer et al. 1988). Excretion of radioactivity in the urine of rats following intratracheal instillation also only accounted for 2.2% of the administered dose at 6 hours (Weyand and Bevan 1986). Amounts of radiolabel in the blood were also very small. However, levels could still be determined in order to derive toxicokinetic parameters. The data obtained by Weyand and Bevan (1986) fit best to a 3-compartment model whereby the half-lives for the three phases were 4.3, 31.5, and 277 minutes.

Results obtained by Weyand and Bevan (1986, 1988) revealed that a large fraction of the administered dose was excreted in the bile. After 6 hours, 53% of the dose was excreted into the intestine and intestinal contents of rats that were without a cannula, while cannulated rats excreted 74% in the bile over the same period.

In general, the rate of benzo(a)pyrene excretion into bile declined as dose increased in rats and guinea pigs. In hamsters, the biliary excretion of benzo(a)pyrene was different from the other species. The rates of radioactivity excretion were similar after administration of either dose. Hence, the major difference between hamsters and other species was that the total fraction of dose excreted after administration of the lower dose of benzo(a)pyrene was lower in hamsters than in other species (Weyand and Bevan 1987b). Metabolites excreted in the bile included thioether conjugates (62.5%), glucuronide conjugates (22.8%), sulfate conjugates (7.4%) and free benzo(a)pyrene (9.8%) (Weyand and Bevan 1988).

2.3.4.2 Oral Exposure

No studies were located in humans regarding the excretion of PAHs following oral exposure. However, as the dose of chrysene in the diet fed to rats increased, the percentage of excreted hydrocarbon also increased. Approximately 79% of the chrysene dose was eliminated by the rat in the feces (Chang 1943). The amount of unchanged hydrocarbon excreted in the feces by the rat that was administered dibenz(a,h)anthracene in the diet or by gavage also increased with dose. Approximately 90% of the dose was excreted in the feces. (Chang 1943).

2.3.4.3 Dermal Exposure

No studies were located regarding the excretion of PAHs in humans following dermal exposure. However, the presence of [^{14}C]-activity in the urine and feces of rats that received [^{14}C]-anthracene applied to the skin provides evidence of its absorption (Yang et al. 1986). At 6 days after administration, the fraction of the dose in the urine and feces was 29.1% and 21.9%, respectively.

2.3.4.4 Other Routes of Exposure

Six hours after intravenous administration of $[^{14}C]$-benzo(a)pyrene to rabbits (0.8 mg/kg), 30% and 12% of the dose was excreted in the bile and urine, respectively. Excretion of the activity into the bile was biphasic over a period of 30 hours with apparent half lives of 0.27 and 4.623 hours for the rapid and slow phases, respectively. Treatment of the bile and urine with beta-glucuronidase and aryl sulfatase increased the amount of activity in the bile and urine that was extractable into ethyl acetate indicating the presence of glucuronide and sulfate conjugates. Intraduodenal administration of the bile resulted in 21 and 14% of the intraduodenal dose being excreted into the bile and urine, respectively. Since biliary metabolites undergo enterohepatic recirculation, the half life for ^{14}C-activity in bile is expected to be longer in animals without biliary fistulae (Chipman et al. 1982).

Weyand and Bevan (1986) reported that the overall elimination of $[^{3}H]$-benzo(a)pyrene following intravenous administration (0.001 mg/kg) best fit a triexponential model, as after inhalation exposure. The half-lives for the three phases were 1.5, 22.4, and 178 minutes. These parameters were very similar to those derived from intratracheal instillation.

2.4 RELEVANCE TO PUBLIC HEALTH

The PAHs occur ubiquitously in the environment from both man-made and natural sources. PAHs occur in the atmosphere most commonly in the products of incomplete combustion. These include fossils fuels; cigarette smoke; industrial processes (such as coke production, refinement of crude oil); and exhaust emissions from gasoline engines, oil-fired heating and burnt coals. PAHs are present in groundwater, surface water, drinking water, wastewater, and sludge. They are found in foods, particularly charbroiled, broiled or pickled food items, and refined fats and oils. Individuals living in the vicinity of hazardous waste sites where PAHs have been detected at levels above background may experience exposure to these chemicals via inhalation of contaminated air, or ingestion of contaminated food, soil, or water.

Evidence exists to indicate that certain PAHs are carcinogenic in humans and animals. The evidence in humans comes primarily from occupational studies where workers involved in such processes as coke production, roofing, oil refining, or coal gasification are exposed to mixtures containing PAHs (e.g., coal tar, coke oven emissions, soot, shale and crude oil). Cancer associated with exposure to PAH-containing mixtures in humans occurs predominantly in the lung and skin following inhalation and dermal exposure, respectively. Some ingestion of PAHs is likely due to swallowing of particulates containing PAHs subsequent to mucociliary clearance from the lung. Certain PAHs have also been shown to induce cancer in animals. The site of tumor induction is influenced by route of administration; i.e., stomach tumors are observed following ingestion, lung tumors following inhalation, and skin tumors following dermal exposure.

Non-cancer adverse health effects associated with PAH exposure have been observed in animals, but (with the exception of adverse hematological and dermal effects) generally not in humans. Animal studies demonstrate that PAHs tend to affect proliferating tissues such as bone marrow, lymphoid organs, gonads and intestinal epithelium. Thus, although PAHs are distributed extensively throughout the body, their major target organs appear to be the hematopoietic and lymphoid systems in animals.

Death. There have been no reports of death in humans following exposure to any of the PAHs. However, benzo(a)pyrene is fatal to mice following ingestion, and death in animals has been reported following parenteral exposure to a number of PAHs. The intraperitoneal LD_{50}s in mice for phenanthrene, pyrene, anthracene, chrysene and benzo(a)pyrene are 700, 680, more than 430, more than 320 and 250 mg/kg body weight, respectively (Gerarde 1960; Salamone et al. 1981). Reduced survival time in "responsive" mice (those capable of producing increased levels of cytochrome P-450 enzymes) was observed following a single intraperitoneal dose of 500 mg/kg benzo(a)pyrene (Robinson et al. 1975). In contrast, oral exposure to benzo(a)pyrene results in reduced survival of "nonresponsive" mice (those whose P-450 enzymes are not induced by PAHs).

While the results in animal studies indicate that exposure to PAHs is lethal, the majority of the data are from parenteral exposure. This route is not applicable to exposure routes humans may expect to encounter, so the relevance of these findings to public health is not known. Parenteral administration bypasses the first-pass effect in the liver that occurs following oral exposure, where PAHs may be expected to be ultimately biotransformed to inactive metabolites more quickly than in other tissues. However, since death has been observed in animals following oral exposure as well, it can be asssumed that acute exposure to high enough doses of the PAHs can be lethal.

Systemic Effects. Adverse noncancer respiratory effects have not been reported in humans. However, benzo(a)pyrene is a potent inducer and inhibitor of certain cytochrome P-450 enzymes in the lungs of animals. Mice intratracheally administered 10 mg/kg benzo(a)pyrene for one day exhibited a significant decrease in lung cytochrome-P-450 content, benzphetamine-N-demethylase (BND) and nitroreductase activities, while statistically significant increases in aryl hydrocarbon hydroxylase (AHH) and 7-ethoxyresorufin-O-deethylase (EROD) were observed (Mitchell et al. 1987).

Inhalation is a significant route of exposure to PAHs in humans. In vitro studies using human lung tumor cells demonstrate that the benzo(a)pyrene-induced cytotoxicity (as measured by protein incorporation or cloning efficiency) observed was most likely due to formation of such reactive products as 7,8-diol-benzo(a)pyrene (Kiefer et al. 1988). This, coupled with the fact that the respiratory system appears to be a target for PAH-induced cancer in humans, suggests that the respiratory system may be a target organ for PAH-induced noncancer adverse effects in humans as well.

PAHs are contained in cigarette smoke, and smoking is a well-established risk factor in the development of atherosclerosis. Arterial smooth muscle cell proliferation, collagen synthesis, lipid accumulation and cellular necrosis are all involved in the pathogenesis of the atherosclerotic plaque. In vitro studies conducted using bovine, rabbit and human smooth muscle cells from arteries demonstrated that benzo(a)pyrene affects some of the aforementioned processes. Cell proliferation was not affected by benzo(a)pyrene, but a decrease in collagen secretion and an increase in cellular toxicity was noted in both the animal and human cell cultures (Stavenow and Pessah-Rasmussen 1988). These results therefore suggest that PAHs may contribute to the pathogenesis of atherosclerosis in humans. This is a particularly relevant health risk for those individuals exposed to high levels of PAHs in the environment and who also smoke cigarettes.

Anthracene has been associated with gastrointestinal toxicity in humans. Humans that consumed laxatives that contained anthracene (anthracene concentration not specified) for prolonged periods were found to have an increased incidence (73.4%) of melanosis of the colon and rectum as compared to those who did not consume anthracene-containing laxatives (26.6%) (Badiali et al. 1985). The authors suggested that the melanosis observed may be attributed to the consumption of anthracene laxatives and not to intestinal stasis. This study is severely limited because of confounding factors such as the existence of other predisposing factors for melanosis and lack of follow-up.

Several PAHs discussed in this profile have been shown to alter enzyme activity in the intestinal mucosa of animals following oral administration, which could conceivably lead to increased production of reactive intermediates and tissue injury. Given the selectivity of PAHs for rapidly proliferating tissues such as gastrointestinal mucosa and the results discussed above, exposure to PAHs (particularly oral) by humans could lead to adverse gastrointestinal effects.

Hematopoietic toxicity has been observed in human patients with primary liver or metastatic breast cancer that have been treated intermittently with mitoxantrone or bisantrene, which are anthracene-containing chemotherapeutics by intravenous injection for nine weeks. Other components of the chemotherapeutic agents were not identified, and the percentage of anthracene in these drugs was not specified. Myelosuppression, consisting of cumulative leukopenia, and thrombocytopenia were the primary effects observed. However, no control groups and concomitant exposure to other ingredients in the therapeutic agents prevent any definitive conclusions regarding the adverse hematological effects associated with anthracene exposure (Falkson et al. 1985).

Adverse hematological effects have been observed in animals as well following exposure to PAHs. For example, administration of a single intraperitoneal dose of benzo(a)pyrene to mice resulted in a small spleen, marked cellular depletion, prominent hemosiderosis and follicles with large lymphocytes. These pathological lesions were associated with death (Shubik and Porta 1957). Death due to adverse hematological effects (e.g., aplastic anemia and pancytopenia resulting in hemorrhage) has also been observed in mice following subchronic oral exposure to benzo(a)pyrene (Levgraverend et al. 1983; Robinson et al. 1975). In addition, it has been shown that benzo(a)pyrene is toxic to cultured bone marrow cells when applied directly (Legraverend et al. 1983).

As discussed above, PAHs tend to exert their adverse effects on rapidly proliferating tissues, such as the bone marrow blood forming elements; and, it is likely that PAH-induced toxicity in this tissue is due to a specific attack on DNA of cells in the S or synthetic phase of mitosis (EPA 1988a).

Although the human data available on PAH-induced hematological toxicity are flawed by confounding factors, they, together with the animal data and the propensity for PAHs to attack rapidly proliferating tissues, indicate that humans exposed to PAHs may be at risk for developing hematological toxicity.

No adverse hepatic effects have been reported in humans following exposure to PAHs. However, hepatic effects have been observed in animals following short-term oral, intraperitoneal or subcutaneous administration of various PAHs. These effects include the induction of preneoplastic hepatocytes, known as gamma-glutamyl transpeptidase foci, induction of carboxylesterase and aldehyde dehydrogenase activity, an increase in liver weight, and stimulation of hepatic regeneration (an indication of a proliferative effect) (Gershbein 1975; Kemena et al. 1988; Robinson et al. 1975; Shubik and Porta 1957; Torronen et al. 1981; Tsuda and Farber 1980). These hepatic changes are not considered serious adverse effects, and their incidence and severity has been shown to correlate with the carcinogenic potency of particular PAHs.

More serious effects indicative of hepatic injury have been observed in animals. For example, an acute intraperitoneal injection of phenanthrene to rats resulted in liver congestion with a distinct lobular pattern, and an increase in serum aspartate aminotransferase, gamma-glutamyl transpeptidase and creatinine (Yoshikawa et al. 1987). Similarly, a single intraperitoneal injection of pyrene resulted in minimal swelling of the liver, but no significant alterations in serum chemistry. Longer-term administration of PAHs has also been reported to result in adverse hepatic effects in animals. Dibenz(a,h)anthracene injected subcutaneously weekly for 40 weeks and pyrene incorporated in the diet resulted in pale, soft and enlarged livers that showed evidence of fatty degeneration and deposition of iron (Hoch-Ligeti 1941; White and White 1939).

Adverse renal effects associated with PAHs have not been reported in humans. However, in animals renal microsomal carboxylesterase induction was noted following ingestion of benzo(a)pyrene, but not after ingestion of anthracene or phenanthracene. A single injection of anthracene or fluorene, had no adverse effect on the kidneys of mice (Shubik and Porta 1957). Dilated tubules were observed in the kidneys of mice administered pyrene in the diet for 25 days (Rigdon and Giannukos 1964); the toxicological significance of this effect is not known. Given the lack of renal toxicity in humans and the limited value of the observations made in animals, the risk to humans for renal toxicity following exposure to PAHs is not known, but may be low.

The skin is susceptible to PAH-induced toxicity in both humans and animals. Regressive verrucae were reported following subchronic application of benzo(a)pyrene to human skin (Cottini and Mazone 1939). Although reversible and apparently benign, these changes were thought to represent neoplastic proliferation. Benzo(a)pyrene application also apparently exacerbated skin lesions in patients with pre-existing skin conditions (pemphigus vulgaris and xeroderma pigmentosum) (Cottini and Mazone 1939). Workers exposed to substances that contain PAHs (e.g., coal tar) experience chronic dermatitis and hyperkeratosis (EPA 1988a).

Adverse dermatological effects have also been noted in animals in conjunction with acute and subchronic dermal exposure to PAHs. These effects include destruction of sebaceous glands, skin ulcerations, hyperplasia and hyperkeratosis (Bock and Mund 1958), and alterations in epidermal cell growth alterations (Elgjo 1968).

The observation that PAHs adversely affected the skin in both humans and animals is not surprising. The skin undergoes rapid cell turnover; and is thus a likely target for PAH attack on DNA synthesis. Given the information discussed above, the ubiquitous nature of PAHs in the environment, and the susceptibility of the skin to PAH-induced toxicity, adverse skin effects may occur in individuals exposed to these chemicals by the dermal route.

As mentioned above, the lymphoid system, because of its rapidly proliferating tissues, is susceptible to PAH-induced toxicity. The mechanism of action for this effect is most likely inhibition of DNA synthesis. No adverse effects on this system associated with PAH exposure have been reported in humans, but several accounts of lymphoid toxicity in animals are available. A single intraperitoneal injection of benzo(a)pyrene to mice resulted in a small spleen with marked cellular depletion, prominent and edematous trabeculae and large lymphocytes. These lesions resulted in death (Shubik and Porta 1957). Lymphoid effects including treatment-related increases in reticulum cells and iron accumulation have been observed in mice following weekly subcutaneous injection of benz(a)anthracene for 40 weeks (Hoch-Ligeti 1941). Subchronic weekly subcutaneous injections of a 0.05% colloidal solution in 1% gelatine dibenz(a,h)anthracene to albino mice for 40 weeks has also resulted in gross changes in the lymphoid system. An increase in reticulum (stem) cells, accumulation of iron, reduced lymphoid cells and dilated lymph sinuses were observed. The reduction of lymphoid cells was more pronounced among dibenz(a,h)anthracene-treated mice by comparison to anthracene and benz(a)anthracene treated animals. Moreover, the weight of the spleens in the treated mice was significantly lower than the spleen weights in the controls (Hoch-Ligeti 1941). Adverse hemolymphatic changes, including the appearance of extravascular red blood cells in the lymph spaces and large pigmented cells were also reported following subcutaneous injections of dibenz(a,h)anthracene to male rats for several weeks. (Lasnitzki and Woodhouse 1944).

Even though these effects have not been noted in humans, the data in animals and the rapidly proliferating nature of this tissue suggest that humans exposed to PAHs may be a risk for the development of adverse effects on the lymphoid system.

Immunological Effects. Immunotoxicity associated with exposure to PAHs has not been observed in humans. There are reports in the literature concerning the immunotoxicity of PAHs following dermal, intraperitoneal and subcutaneous injection in animals. The carcinogenic PAHs as a group have an immunosuppressive effect, and, in general, the degree of immunosuppression correlates with the carcinogenic potency.

Benzo(a)pyrene has been shown to markedly inhibit the immune system, especially T-cell dependent antibody production by lymphocytes exposed either _in vivo_ or _in vitro_ (Blanton et al. 1986; Lyte and Bick 1985; White and Holsapple 1984).

The immunocytotoxic effects of benzo(a)pyrene were observed in C3H and C57Bl mice intraperitoneally injected with P-815 tumor target cells followed 10 days later by intraperitoneal injection with benzo(a)pyrene. A consistently decreasing relationship was noted between the dose of benzo(a)pyrene and both the binding and killing of target cells for splenic and peritoneal lymphocytes. The authors indicate that lymphocyte mediated immunity may be inhibited by PAHs and that this immunosuppressant effect can contribute to their carcinogenicity (Wojdani et al. 1984).

Benzo(a)pyrene-induced immune suppression was reported in male B6C3Fl mice (Lyte and Bick 1985) and in the offspring of C3H/Anf mice treated intraperitoneally with benzo(a)pyrene (Urso and Gengozian 1980). Subcutaneous injections of benzo(a)pyrene in female B6C3Fl mice produced a dose-related suppression of antibody production to both T-cell-independent and T-cell-dependent antigens (White and Holsapple 1984). A reduction in target cell killing by lymphocytes for two mouse strains was observed after a single intraperitoneal injection of benzo(a)pyrene (Wojdani et al. 1984).

Benzo(a)pyrene exerts its inhibitory effects on antibody production through alterations on the normal functioning of macrophages, T cells and B cells (Blanton et al. 1988). In contrast, benzo(a)pyrene has no effect on most cellular immune responses before the appearance of tumors (Dean et al. 1983b) although benzo(a)pyrene exposure does inhibit IL-2 dependent proliferation (Myers et al. 1988). Mice treated with high doses of dibenz(a,h)anthracene exhibited a reduced serum antibody level in response to antigenic challenge by comparison to controls (Malmgren et al. 1952).

The immunosuppressive effects of dibenz(a,h)anthracene were studied in both AHH inducible mice (C57Bl/6) and AHH noninducible mice (DBA/2N) by intraperitoneal and oral administration (Lubet et al. 1984). Immunosuppression occurred in both strains and was more pronounced in the C57Bl/6 mice than in the DBA/2N mice, following i.p. administration. However, the DBA/2N mice were more susceptible to immunosuppression following oral administration. These results suggest that PAHs are rapidly metabolized and excreted following oral administration in AHH inducible mice, whereas in noninducible mice the PAHs are absorbed and distributed to target organs. Based on these results, the authors concluded that AHH inducibility plays an important role in the immunosuppressive activity of PAHs.

Given the high potential for exposure to PAHs in the vicinity of hazardous waste sites, the evidence from animal studies, and the heterogeneity of human genotypes with regard to enzyme induction capabilities, it would be prudent to consider that PAHs may pose an immunotoxic risk to humans living in areas surrounding hazardous waste sites.

Neurological Effects. No information is available on the short- or long-term neurotoxic effects of exposure to PAHs in humans and animals. However, acute, intermediate or chronic duration studies conducted in animals do not indicate that any of the PAHs tested showed evidence of neurotoxicity, although these tests were not designed to detect subtle neurological changes.

Developmental Effects. The developmental toxicity data for the PAHs are mostly limited to in utero exposure of pregnant animals to benzo(a)pyrene via various routes of exposure. The placental transfer of benzo(a)pyrene has been shown in mice following oral and intravenous exposure of dams (Shendrikova et al. 1974), and in rats via the intratracheal (Srivastava et al. 1986) route of administration. The available data from oral studies in animals indicate that exposure of pregnant dams to benzo(a)pyrene produced resorptions and malformations in fetuses (Legraverend et al. 1984) and sterility in F1 mouse progeny (Mackenzie and Angevine 1981). Pre- and post-implantation losses, and decreased fetal weights and survival were reported in rats (Sheveleva 1978). No more details were available for this study. Investigations by Legraverend et al. (1984) suggest that benzo(a)pyrene metabolites generated in the fetus rather than in the maternal tissues are responsible for these adverse effects. Also the genetic differences observed in this study using the oral route were contrary to those induced by intraperitoneal administration of benzo(a)pyrene (Hoshino et al. 1981; Shum et al. 1979), thus emphasizing the importance of route of administration in benzo(a)pyrene metabolism and resulting toxicity.

The developmental effects of benzo(a)pyrene have also been investigated in animals using the parenteral route of administration. Intraperitoneal injection of benzo(a)pyrene to pregnant mice produced stillbirths, resorptions and malformations at a greater incidence in Ah-responsive mice than Ah-nonresponsive mice (Shum et al. 1979); testicular changes including atrophy of seminiferous tubules with lack of spermatids and spermatozoa; interstitial cell tumors (Payne 1958); immunosuppression (Urso and Gengozian 1980); and tumor induction (Bulay and Wattenberg 1971, Soyka 1980). Adverse effects observed following subcutaneous injection of benzo(a)pyrene include increased fetal resorptions in rats (Wolfe and Bryan 1939) and lung tumor induction in mice (Nikonova 1977). Decreased fetal survival (Wolfe and Bryan 1939) and lung tumor development (Rossi et al. 1983) were reported in Swiss mice following direct intra-embryonal injection of benzo(a)pyrene. The relevance of findings in animal studies with regard to human exposure is that benzo(a)pyrene may produce adverse effects in the unborn and offspring of women exposed to benzo(a)pyrene. Furthermore, the results of genetic studies conducted via oral and intraperitoneal routes emphasize the importance of route of administration in benzo(a)pyrene metabolism and resulting toxicity. Based on these observations, it is therefore prudent to consider that the genetically heterogeneous human population may show variation in response to in utero exposure to benzo(a)pyrene.

The other PAHs such as anthracene, benzanthracene, chyrsene and dibenz(a,h)anthracene have also been tested for developmental effects via parenteral routes. Of these compounds dibenz(a,h)anthracene produced fetolethal effects in rats (Wolfe and Bryan 1939) while chrysene produced liver tumors in the mouse progeny (Buening et al. 1979a; Grover et al. 1975)

The implications of the findings in animals studies are that adverse effects may occur in the unborn and offspring of women exposed to benzo(a)pyrene. Furthermore, the severity of the effect may vary depending upon the genotype of the individual exposed (see Section 2.8, Populations That Are Unusually Susceptible).

Reproductive Effects. In both prospective and retrospective studies, a decrease in fecundity was observed in women who were exposed prenatally to cigarette smoke (i.e. their mothers smoked while they were pregnant) (Weinberg et al. 1989; Wilcox et al. 1989). This association was apparent even after adjustment for age, frequency of intercourse, current smoking status, age at menarche, childhood exposure to cigarette smoking, educational level, reproductive history, body weight, and consumption of alcohol and caffeine. On the other hand, an increase in fecundity was observed in a retrospective study of women who were exposed to cigarette smoke in early childhood. These apparently opposite effects may be partially explained by the fact that when a woman smokes during pregnancy, her fetus is exposed to the components of the cigarette smoke that cross the placenta as well as changes in fetal and placental oxygenation and metabolism that are secondary to changes in maternal metabolism resulting from smoking. However, childhood exposure involves direct inhalation of cigarette smoke. The authors could offer no explanation as to why fecundity should be increased as a result of childhood exposure to cigarette smoke (Weinberg et al. 1989; Wilcox et al. 1989).

The testes and ovaries contain rapidly proliferating cells and therefore should be considered susceptible to damage by PAHs. The reproductive toxicity data in animals for the PAHs are limited. The available animal studies exclusively discuss the reproductive effects of benzo(a)pyrene. Adverse effects such as decreased fertility and total sterility in Fl progeny of CD-1 mice (Mackenzie and Angevine 1981) and decreased incidence of pregnant female rats at parturition (Rigdon and Rennels 1964) were reported following oral exposure to benzo(a)pyrene. However, no adverse reproductive effects were observed in Swiss mice fed benzo(a)pyrene in their diet (Rigdon and Neal 1965). The metabolic differences and method of benzo(a)pyrene administration could account for the differential response to benzo(a)pyrene induced toxicity in these studies. Single intraperitoneal injection of benzo(a)pyrene to female C57Bl/6N mice decreased the number of corpora lutea (Swartz and Mattison 1985). The antiestrogenic effects causing decreased uterine weights in pseudopregnant Sprague-Dawley rats were reported following daily subcutaneous injections of benzo(a)pyrene during day 6 to 11 of pseudopregnancy (Bui et al. 1986). Similar treatment to pregnant rats during gestation period caused resorptions, reduced percentage of viable litters and decreased uterine weights (Bui et al. 1986). The studies conducted on the reproductive effects of benzo(a)pyrene via parenteral routes are briefly discussed below.

Single intraperitoneal injection of benzo(a)pyrene to female C57BL/6N mice at doses as high as 500 mg/kg body weight produced a dose- and time-dependent decrease in the number of corpora lutea (Swartz and Mattison 1985). The NOAEL in this study was 1 mg/kg/day. These results demonstrate the sensitivity of integrated hypothalamic-pituitary-ovarian function to adverse effects of benzo(a)pyrene. Animal studies have shown that benzo(a)pyrene is sufficiently absorbed in the body when exposed via various routes.

Daily subcutaneous injection of benzo(a)pyrene beginning on day 6 of gestation for six as opposed to three days significantly increased the number of resorptions, and decreased the fetal survival and uterine weights in Sprague-Dawley rats (Bui et al. 1986). In pseudopregnant (i.e. condition occurring following sterile matings in which anatomical and physiological changes occur similar to those of pregnancy) rats, similar benzo(a)pyrene treatment during days 6 to 11 of pseudopregnancy significantly decreased the cyclic nucleotide levels and uterine weights suggesting an antiestrogenic effect (Bui et al. 1986). Use of a single dosage level precluded the assessment of dose-response in these studies. The relevance of these findings with regard to human exposure is that the probability that adverse reproductive effects may occur in humans exposed to benzo(a)pyrene at workplace or at hazardous waste sites may be increased.

Genotoxic Effects. Tables 2-4 and 2-5 present the results of in vitro and in vivo genotoxicity studies, respectively. The data indicate that several PAHs have some genotoxic potential and that a mammalian metabolic activation system is necessary for activity in most cases. All but three chemicals (acenaphthene, acenaphthylene, and fluorene) were reported to be mutagenic in at least one in vitro assay with the bacteria Salmonella typhimurium. The evidence for genotoxic activity in other test systems varies greatly by chemical.

Benzo(a)pyrene is the most widely tested PAH. It is genotoxic in a large number and a wide variety of in vitro and in vivo assays. There were no tests reported for humans exposed to benzo(a)pyrene in vivo, but the results of in vitro assays with human cells suggest that it is likely to have genotoxic effects in humans. Several types of cultured human tissue cells demonstrated positive results for benzo(a)pyrene-induced genotoxicity (as evidenced by the induction of chromosomal aberrations, sister chromatid exchange), and binding of benzo(a)pyrene to DNA (Table 2-4). Benzo(a)pyrene also produced several different types of genotoxic effects (e.g. DNA binding and damage, sister chromatid exchange, chromosomal aberrations and cell transformation) in two types of non-human in vitro systems, bacteria and mammalian cells (Table 2-4).

The results of in vivo studies indicate that benzo(a)pyrene produces many of the same types of genotoxic effects observed in in vitro studies in intact mice, rats, and hamsters. The available data indicate that benzo(a)pyrene induced genotoxic effects in both somatic and germ cells of the intact exposed animals (Table 2-5). It is not known if benzo(a)pyrene is capable of producing these effects in human germ cells.

Both benz(a)anthracene and dibenz(a,h)anthracene were mutagenic (Barfknecht et al. 1982; Rocchi et al. 1980) and produced DNA damage (Martin et al. 1978) in cultured human cells. The majority of the test results in non-human systems were also positive. Thus, the weight of the evidence indicates that these two chemicals are genotoxic also, and that they may produce genotoxic effects in human cells.

There is some evidence that benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(ghi)perylene, chrysene, fluoranthene and indeno(1,2,3-c,d)pyrene are genotoxic, but the strength of the conclusions that can be drawn for these chemicals is limited by the small number of studies reported. Of these chemicals, genotoxic effects in human cells have been reported only for chrysene and fluoranthene. Both chemicals were mutagenic in human

TABLE 2-4. Genotoxicity of PAHs *In Vitro*

End Point	Species or Test System	Results: With Activation	Results: Without Activation	Reference
	ACENAPHTHENE			
Prokaryotic organisms: Gene mutation	*Salmonella typhimurium*	-	ND	Pahlman and Pelkonen 1987
	ACENAPHTHYLENE			
Prokaryotic organisms: Gene mutation	*S. typhimurium*	-	ND	Bos et al. 1988
	ANTHRACENE			
Prokaryotic organisms: Gene mutation	*S. typhimurium*	+	-	Sakai et al. 1985
	S. typhimurium	+	ND	Carver et al. 1986
	S. typhimurium	-	-	Simmon 1979a; LaVoie et al. 1985; Rosenkranz and Poirier 1979; LaVoie et al. 1983b
	S. typhimurium	-	ND	Pahlman and Pelkonen 1987; Bos et al. 1988; LaVoie et al. 1979
DNA damage	*Escherichia coli*/Pol A	-	-	Rosenkranz and Poirier 1979
	E. coli WP2-WP100/rec- assay	-	ND	Mamber et al. 1983
	E. coli/differential killing	-	-	Tweats 1981
Eukaryotic organisms: Fungi: Mitotic recombination	*Saccharomyces cerevisiae* D3	-	-	Simmon 1979b
Gene conversion	*S. cerevisiae* D4-RDII	ND	-	Siebert et al. 1981
Mammalian cells: Gene mutation	Fischer rat embryo cells	ND	-	Mishra et al 1978
	Mouse lymphoma L5178Y/$TK^{+/-}$	(+)	ND	Amacher and Turner 1980
	Mouse lymphoma L5178Y/$TK^{+/-}$	-	ND	Amacher et al. 1980
	Human lymphoblasts TK6	-	ND	Barfknecht et al. 1982
	Human epithelial cells EUE	ND	-	Rocchi et al. 1980

TABLE 2-4 (Continued)

End Point	Species or Test System	Results With Activation	 Without Activation	Reference
DNA damage	HeLa cells/unscheduled DNA synthesis	-	-	Martin et al. 1978
	Human skin fibroblasts	ND	-	Milo et al. 1978
Chromosome aberrations	Rat liver cells RL1	ND	-	Dean 1981
Sister chromatid exchange	Rat liver cells ARL18	ND	-	Tong et al. 1981
Transformation	Hamster BHK21 clone 13	-	ND	Greb et al. 1980
	Syrian hamster embryo cells	ND	-	Dunkel et al. 1981
	Mouse C3H/10T$^{1/2}$ clone 8	-	ND	Dunkel et al. 1981
	Mouse Balb/3T3 cells	ND	-	Peterson et al. 1981; Lubet et al. 1983b
	Fischer rat embryo cells	ND	-	Mishra et al. 1978
	Fischer rat embryo cells/leukemia virus transformation	ND	-	Dunkel et al. 1981
	BENZ(a)ANTHRACENE			
Prokaryotic organisms: Gene mutation	S. typhimurium	+	-	Norpoth et al. 1984; Simmon 1979a
	S. typhimurium	+	ND	Pahlman and Pelkonen 1987; Coombs et al. 1976; Bos et al. 1988; Hermann 1981; Carver et al. 1986
	S. typhimurium	-	-	Rosenkranz and Poirier 1979
DNA damage	E. coli/Pol A	-	-	Rosenkranz and Poirier 1979
Eukaryotic organisms: Fungi: Mitotic recombination	S. cerevisiae D3	-	-	Simmon 1979b

TABLE 2-4 (Continued)

End Point	Species or Test System	Results		Reference
		With Activation	Without Activation	
Mammalian cells: Gene mutation	Mouse lymphoma L5178Y/$TK^{+/-}$	+	ND	Amacher et al. 1980
	Mouse lymphoma L5178Y/$TK^{+/-}$	+	-	Amacher and Turner 1980; Amacher and Paillet 1982
	Mouse lymphoma L5178Y/$TK^{+/-}$	-	-	Amacher and Paillet 1983
	Chinese hamster V79	-	-	Huberman 1975
	Chinese hamster V79	-	ND	Huberman 1975
	Human lymphoblasts TK6	+	ND	Barfknecht et al. 1982
	Human epithelial cells EUE	ND	-	Rocchi et al. 1980
	Human keratinocytes	ND	-	Allen-Hoffmann and Rheinwald 1984
DNA damage DNA synthesis	HeLa cells/unscheduled	+	NR	Martin et al. 1978
Sister chromatid exchange	Rat liver cells ARL18	ND	(+)	Tong et al. 1981
Transformation	Hamster BHK21 clone 13	+	ND	Greb et al. 1980
	Hamster embryo cells	ND	(+)	DiPaolo et al. 1969/1971
	Hamster embryo cells	-	ND	Grover et al. 1971
	Syrian hamster embryo cells	ND	+	Dunkel et al. 1981
	Syrian hamster lung cells FSHL	ND	+	Emura et al 1980
	Mouse ventral prostate C3H clone G23	ND	-	Marquardt et al. 1972; Grover et al. 1971
	Mouse Balb/3T3 cells	ND	(+)	Dunkel et al. 1981
	Fischer rat embryo cells/leukemia virus transformation	ND	+	Dunkel et al. 1981
	BENZO(b)FLUORANTHENE			
Prokaryotic organisms: Gene mutation	S. typhimurium	+	ND	Amin et al. 1984; Hermann 1981; LaVoie et al. 1979

TABLE 2-4 (Continued)

End Point	Species or Test System	Results With Activation	 Without Activation	Reference
	S. typhimurium	-	ND	Mossanda et al. 1979
	S. typhimurium/fluctuation test	-	ND	Mossanda et al. 1979
Mammalian cells: Gene mutation	Chinese hamster V79	-	-	Huberman 1975
Transformation	Hamster BHK21 clone 13	+	ND	Greb et al. 1980
	Syrian hamster lung cells FSHL	ND	+	Emura et al. 1980
	BENZO(k)FLUORANTHENE			
Prokaryotic organisms: Gene mutation	S. typhimurium	+	ND	LaVoie et al. 1980; Amin et al. 1985b; LaVoie et al. 1979
Mammalian cells: Transformation	Syrian hamster lung cells FSHL	ND	-	Emura et al. 1980
	BENZO(ghi)PERYLENE			
Prokaryotic organisms: Gene mutation	S. typhimurium	+	-	Sakai et al. 1985
	S. typhimurium	+	ND	Mossanda et al. 1979; Carver et al. 1986; LaVoie et al. 1979
	S. typhimurium/fluctuation test	(+)	ND	Mossanda et al. 1979
	BENZO(a)PYRENE			
Prokaryotic organisms: Gene mutation	S. typhimurium	+	-	Prasanna et al. 1987; Sakai et al. 1985; Simmon 1979a; Glatt et al. 1987; Rosenkranz and Poirier 1979

TABLE 2-4 (Continued)

End Point	Species or Test System	Results: With Activation	Results: Without Activation	Reference
	S. typhimurium	+	ND	Norpoth et al. 1984; Lee and Lin 1988; Alzieu et al. 1987; Pahlman and Pelkonen 1987; Carver et al. 1986; Bos et al. 1988; Hermann 1981; Bruce and Heddle 1979; Marino 1987; Alfheim and Randahl 1984; LaVoie et al. 1979
	S. typhimurium TM677	+	-	Rastetter et al. 1982
	S. typhimurium TM677	+	ND	Babson et al. 1986
DNA damage	E. coli WP2-WP100/rec- assay	+	ND	Mamber et al. 1983
	E. coli/PoLA	+	-	Rosenkranz and Poirier 1979
	E. coli/differential killing	+	-	Tweats 1981
Eukaryotic organisms: Fungi: Mitotic recombination	S. cerevisiae D3	-	-	Simmon 1979b
	S. cerevisiae D4-RDII	ND	-	Siebert et al. 1981
Animal systems: Gene mutation	Chinese hamster V79	+	ND	Arce et al. 1987; Diamond et al. 1980; Huberman 1975
	Chinese hamster V79	+	-	Huberman 1975
	Chinese hamster CHO	+	(+)	Gupta and Singh 1982
	Fischer rat embryo cells/OUA^R	ND	+	Mishra et al. 1978
	Mouse lymphoma L5178Y/TK$^{+/-}$	+	-	Amacher and Paillet 1983; Clive et al. 1979
	Mouse lymphoma L5178Y/TK$^{+/-}$	+	ND	Amacher et al. 1980; Arce et al. 1987; Amacher and Turner 1980
	Mouse lymphoma L5178Y/HGPRT	(+)	ND	Clive et al. 1979
	Human lymphoblasts AHH	ND	+	Crespi et al. 1985

TABLE 2-4 (Continued)

End Point	Species or Test System	Results		Reference
		With Activation	Without Activation	
DNA damage	Human lymphoblasts TK6	+	ND	Crespi et al. 1985
	Human epithelial cells EUE	ND	+	Rocchi et al. 1980; Barfknecht et al. 1982
	Human fibroblasts HSC172	+	-	Gupta and Goldstein 1981
	Human keratinocytes	ND	+	Allen-Hoffmann and Rheinwald 1984
	Rat hepatocytes/DNA repair	ND	+	Williams et al. 1982
	Mouse C3H/10T$^{1/2}$ clone 8	ND	(+)	Lubet et al. 1983b
	HeLa cells/unscheduled DNA synthesis	+	NR	Martin et al. 1978
	Human skin fibroblasts	ND	+	Milo et al. 1978
	Human mammary cells	ND	+	Leadon et al. 1988
	Human fibroblasts/unscheduled DNA synthesis	+	ND	Agrelo and Amos 1981
	Human fibroblasts WI-38/ unscheduled DNA synthesis	+	-	Robinson and Mitchell 1981
DNA binding	Calf thymus DNA	+	ND	Cavalieri et al. 1988a
	Chick embryo fibroblasts	ND	+	Liotti et al. 1988
	Chick embryo hepatocytes	ND	+	Liotti et al. 1988
	Chinese hamster V79	+	ND	Arce et al. 1987
	Mouse lymphoma L5178Y/TK$^{+/-}$	+	ND	Arce et al. 1987
	Mouse C3H/10T$^{1/2}$	ND	+	Arce et al. 1987
	Syrian hamster embryo SHE	ND	+	Arce et al. 1987
	Rat bladder epithelial cells	ND	+	Moore et al. 1982
	Rat mammary epithelial cells	ND	+	Moore et al. 1987
	Human liver HepG2 cells	ND	+	Diamond et al. 1980
	Human mammary cells	ND	+	Moore et al. 1987; Leadon et al. 1988

TABLE 2-4 (Continued)

End Point	Species or Test System	Results		Reference
		With Activation	Without Activation	
	Human bladder cells	ND	+	Moore et al. 1982
	Human endometrial cells	ND	+	Dorman et al. 1981
	Human bronchus cells	ND	+	Harris et al. 1984
	Human colon cells	ND	+	Harris et al. 1984
Chromosome aberrations	Chinese hamster V79-4	-	-	Popescu et al. 1977
	Chinese hamster CHL	+	-	Matsuoka et al. 1979
	Mouse lymphoma L5178Y/TK$^{+/-}$	+	ND	Arce et al. 1987
	Rat liver cells RL1	ND	+	Dean 1981
	Human fibroblasts WI-38	+	-	Weinstein et al. 1977
Sister chromatid exchange	Chinese hamster V79	+	ND	Arce et al. 1987
	Chinese hamster V79	+	-	Popescu et al. 1977; Wojciechowski et al. 1981
	Chinese hamster Don-6	ND	+	Abe et al. 1983b
	Chinese hamster CHO	+	-	Husgafvel-Pursiainen et al. 1986
	Rat pleural mesothelial cells	ND	+	Achard et al. 1987
	Rat liver cells ARL18	ND	+	Tong et al. 1981
	Rat hepatoma Reuber H4-II-E	ND	+	Dean et al. 1983a
	Rat esophageal tumor R1	ND	+	Abe et al. 1983b
	Rat ascites hepatoma AH66-B	ND	+	Abe et al. 1983b
	Human fibroblasts TIG-II	+	(+)	Huh et al. 1982
	Human hepatoma C-HC-4	ND	+	Abe et al. 1983a and b
	Human hepatoma C-HC-20	ND	+	Abe et al. 1983a and b
Transformation	Golden hamster embryo cells	+	ND	Mager et al. 1977
	Hamster BHK21 clone 13	+	-	Greb et al. 1980

TABLE 2-4 (Continued)

End Point	Species or Test System	Results		Reference
		With Activation	Without Activation	
	Hamster embryo cells/SA7 virus transformation	ND	+	Casto et al. 1977
	Syrian hamster embryo cells	ND	+	DiPaolo et al. 1969/1971; Dunkel et al. 1981
	Syrian hamster embryo cells/focus assay	ND	+	Casto et al. 1977
	Syrian hamster lung FSHL	ND	+	Emura et al. 1980; 1987
	Syrian hamster SHE/SA7 virus transformation	ND	+	Arce et al. 1987
	Mouse C3H/10T$^{1/2}$	ND	+	Arce et al. 1987; Lubet et al. 1983b; Peterson et al. 1981
	Mouse Balb/3T3	ND	+	Dunkel et al. 1981
	Mouse Balb/3T3 clone A31-1-1	ND	+	Little and Vetroys 1988
	Fischer rat embryo cells	ND	+	Mishra et al. 1978
	Rat embryo cells/SA7 virus transformation	ND	+	DiPaolo and Casto 1976
	Fischer rat embryo cells/leukemia virus transformation	ND	+	Dunkel et al. 1981
	CHRYSENE			
Prokaryotic systems Gene mutation	S. typhimurium	+	-	Sakai et al. 1985
	S. typhimurium	+	ND	Bos et al. 1988; Hermann 1981; Carver et al. 1966; Pahlman and Pelkonen 1987; LaVoie et al. 1979
	S. typhimurium	(+)	ND	Wood et al. 1977
	S. typhimurium	-	-	Simmon 1979a; Rosenkranz and Poirier 1979
DNA damage	E. coli/PolA	-	-	Rosenkranz and Poirier 1979

TABLE 2-4 (Continued)

End Point	Species or Test System	Results		Reference
		With Activation	Without Activation	
Eukaryotic organisms:				
Fungi:				
Mitotic recombination	*S. cerevisiae* D3	-	-	Simmon 1979b
	S. cerevisiae D4-RDII	ND	-	Siebert et al. 1981
Mammalian cells:				
Gene mutation	Chinese hamster V79	-	ND	Huberman 1975
	Human lymphoblasts TK6	+	ND	Barfknecht et al. 1982
	Human epithelial cells EUE	ND	-	Rocchi et al. 1980
Transformation	Hamster BHK21 clone 13	+	ND	Greb et al. 1980
	Mouse ventral prostate C3H clone G23	ND	-	Marquardt et al. 1972
	DIBENZ(a,h)ANTHRACENE			
Prokaryotic systems:				
Gene mutation	*S. typhimurium*	+	ND	Wood et al. 1978; Pahlman and Pelkonen 1987; Carver et al. 1986; Hermann 1981
Eukaryotic organisms:				
Fungi:				
Gene mutation	*Neurospora crassa*	ND	+	Barrat and Tatam 1958
Mitotic recombination	*S. cerevisiae* D4-RDII	ND	-	Siebert et al. 1981
Mammalian cells:				
Gene mutation	Chinese hamster V79	(+)	ND	Huberman 1975
	Human epithelial cells EUE	ND	(+)	Rocchi et al. 1980
DNA damage DNA synthesis	HeLa cells/unscheduled	+	NR	Martin et al. 1978
DNA binding	Human bronchus cells	ND	+	Harris et al. 1984
Transformation	Hamster embryo cells	-	ND	Grover et al. 1971
	Hamster embryo cells/SA7 virus transformation	ND	+	Casto 1973; Casto et al. 1977
	Syrian hamster embryo cells	ND	+	DiPaolo et al. 1969
	Syrian hamster embryo cells/focus assay	ND	+	Casto et al. 1977

TABLE 2-4 (Continued)

End Point	Species or Test System	Results: With Activation	Results: Without Activation	Reference
	Hamster BHK21 clone 13	+	-	Greb et al. 1980
	Mouse ventral prostate C3H clone G23	ND	-	Marquardt et al. 1972
	Mouse C3H/10T$^{1/2}$ clone 8	ND	(+)	Lubet et al. 1983b
	Rat embryo cells/SA7 virus transformation	ND	+	DiPaolo and Casto 1976
	FLUORANTHENE			
Prokaryotic organisms: Gene mutation	*S. typhimurium*	+	ND	Carver et al. 1986; Bos et al. 1988; Hermann 1981; LaVoie et al. 1979
	S. typhimurium	(+)	ND	Bos et al. 1987
	S. typhimurium	-	ND	Mossanda et al. 1979
	S. typhimurium/fluctuation test	+	ND	Mossanda et al. 1979
	S. typhimurium/fluctuation test	+	-	Bhatia et al. 1987
	S. typhimurium/taped plate assay	+	-	Bos et al. 1987
	S. typhimurium TM677	+	-	Rastetter et al. 1982
	S. typhimurium TM677	+	ND	Babson et al. 1986
Mammalian cells: Gene mutation	Human lymphoblasts AHH1	ND	-	Crespi et al. 1985
	Human lymphoblasts TK6	+	ND	Barfknecht et al. 1982
Sister chromatid exchange	Chinese hamster CHO-1	+	-	Palitti et al. 1986
	FLUORENE			
Prokaryotic organisms: Gene mutation	*S. typhimurium*	-	-	Sakai et al. 1985
	S. typhimurium	-	ND	Bos et al. 1988; Hermann 1981; Pahlman and Pelkonen 1987; LaVoie et al. 1979
DNA damage	*E. coli* WP2-WP100/rec- assay	-	ND	Mamber et al. 1983

TABLE 2-4 (Continued)

End Point	Species or Test System	Results: With Activation	Results: Without Activation	Reference
	INDENO(1,2,3-c,d)PYRENE			
Prokaryotic organisms: Gene mutation	S. typhimurium	+	-	Rice et al. 1985b
	S. typhimurium	+	ND	LaVoie et al. 1979
Mammalian cells: Transformation cells FSHL	Syrian hamster lung	ND	+	Emura et al. 1980
	PHENANTHRENE			
Prokaryotic organisms: Gene mutation	S. typhimurium	+	-	Sakai et al. 1985
	S. typhimurium	+	ND	Oesch et al. 1981; Carver et al. 1986
	S. typhimurium	(+)	ND	Bos et al. 1988
	S. typhimurium	-	-	Simmon 1979a; LaVoie et al. 1981; Rosenkranz and Poirier 1979
	S. typhimurium	-	ND	Pahlman and Pelkonen 1987; Hermann 1981; LaVoie et al. 1979
DNA damage	E. coli/PolA	-	-	Rosenkranz and Poirier 1979
Eukaryotic organisms: Fungi Mitotic recombination	S. cerevisiae D3	-	-	Simmon 1979b
	S. cerevisiae D4-RDII	ND	-	Siebert et al. 1981
Mammalian cells: Gene mutation	Fischer rat embryo cells	ND	-	Mishra et al. 1978
	Chinese hamster V79	-	ND	Huberman 1975
	Human lymphoblasts TK6	(+)	ND	Barfknecht et al. 1982
DNA damage	Human skin fibroblasts	ND	-	Milo et al. 1978

TABLE 2-4 (Continued)

End Point	Species or Test System	Results		Reference
		With Activation	Without Activation	
Chromosome aberrations	Chinese hamster V79-4	-	-	Popescu et al. 1977
	Chinese hamster Don	ND	-	Abe and Sasaki 1977
	Chinese hamster CHL	ND	-	Ishidate and Odashima 1977
	Chinese hamster CHL	-	-	Matsuoka et al. 1979
Sister chromatid exchange	Chinese hamster V79-4	-	-	Popescu et al. 1977
	Chinese hamster Don	ND	-	Abe and Sasaki 1977
Transformation	Syrian hamster embryo cells	ND	-	DiPaolo et al. 1969; Dunkel et al. 1981
	Hamster BHK21 clone 13	-	ND	Greb et al. 1980
	Hamster embryo cells/ SA7 virus transformation	ND	-	Casto et al. 1977
	Mouse ventral prostate C3H clone G23	ND	-	Marquardt et al. 1972
	Mouse C3H/10T$^{1/2}$	ND	-	Peterson et al. 1981; Lubet et al. 1983b
	Mouse Balb/3T3 cells	ND	-	Dunkel et al. 1981
	Fischer rat embryo cells	ND	-	Mishra et al. 1978
	Fischer rat embryo cells/ leukemia virus transformation	ND	-	Dunkel et al. 1981
	PYRENE			
Prokaryotic organisms: Gene mutation	S. typhimurium	+	-	Sakai et al. 1985
	S. typhimurium	+	ND	Bos et al. 1988
	S. typhimurium	-	ND	Carver et al. 1986; Hermann 1981; LaVoie et al. 1979
	S. typhimurium/ fluctuation test	+	+	Bhatia et al. 1987
	S. typhimurium/taped plate	+	ND	Bos et al. 1988

TABLE 2-4 (Continued)

End Point	Species or Test System	Results With Activation	 Without Activation	Reference
DNA damage	E. coli WP2-WP100/rec- assay	-	ND	Mamber et al. 1983
	E. coli/differential killing	-	-	Tweats 1981
Mammalian cells: Gene mutation	Fischer rat embryo cells	ND	+	Mishra et al. 1978
	Chinese hamster V79	-	-	Huberman 1975
	Chinese hamster V79	-	ND	Huberman 1975
	Mouse lymphoma L5178Y/TK$^{+/-}$	-	ND	Amacher et al. 1980
	Human lymphoblasts TK6	-	ND	Barfknecht et al. 1982
DNA damage DNA synthesis	HeLa cells/unscheduled	-	-	Martin et al. 1978
	Rat hepatocytes/DNA repair	ND	-	Williams et al. 1982
	Human skin fibroblasts	ND	-	Milo et al. 1978
	Human skin fibroblasts	-	ND	Agrelo and Amos 1981
	Human fibroblasts WI-38/ unscheduled DNA synthesis	+	-	Robinson and Mitchell 1981
Chromosome aberrations	Chinese hamster V79-4	+	-	Popescu et al. 1977
	Human fibroblasts WI-38	-	-	Weinstein et al. 1977
	Rat liver cells RL1	ND	-	Dean 1981
Sister chromatid exchange	Chinese hamster V79-4	-	-	Popescu et al. 1977
	Rat liver cells ARL18	ND	-	Tong et al. 1981
Transformation	Syrian hamster embryo cells	ND	-	DiPaolo et al. 1969
	Fischer rat embryo cells	ND	-	Mishra et al. 1978
	Hamster embryo cells/ SA7 virus transformation	ND	-	Casto et al. 1977

ND = Not tested; - = negative result; + = positive result; (+) = equivocal or weakly positive result.

TABLE 2-5. Genotoxicity of PAHs *In Vivo*

End Point	Species (Test System)	Results	Reference
	ANTHRACENE		
Mammalian systems:			
Chromosome aberrations	Chinese hamster/bone marrow	-	Roszinsky-Kocher et al. 1979
Sister chromatid exchange	Chinese hamster/bone marrow	-	Roszinsky-Kocher et al. 1979
Micronuclei	Mouse/bone marrow	-	Salamone et al. 1981
Sperm abnormalities	Mouse	-	Topham 1980
Host-mediated systems:			
Gene mutation	*Salmonella typhimurium*/ mouse host-mediated	(+)[a]	Simmon et al. 1979
	Saccharomyces cerevisiae/ mouse host-mediated	-	Simmon et al. 1979
Sister chromatid exchange	Chinese hamster V79 cells/ mouse host-mediated	-	Sirianni and Huang 1978
	BENZ(a)ANTHRACENE		
Mammalian systems:			
Chromosome aberrations	Chinese hamster/bone marrow	-	Roszinsky-Kocher et al. 1979
Sister chromatid exchange	Chinese hamster/bone marrow	+	Roszinsky-Kocher et al. 1979
Insect systems:			
Gene mutation	*Drosophila melanogaster*/ sex-linked recessives	-	Zijlstra and Vogel 1984
	D. melanogaster/ somatic mutation	-	Fahmy and Fahmy 1980
Host-mediated systems:			
Gene mutation mouse host-mediated	*S. typhimurium*/	+	Simmon et al. 1979
	S. cerevisiae/ mouse host-mediated	-	Simmon et al. 1979
	BENZO(b)FLUORANTHENE		
Mammalian systems:			
Chromosome aberrations	Chinese hamster/bone marrow	-	Roszinsky-Kocher et al. 1979

TABLE 2-5 (Continued)

End Point	Species (Test System)	Results	Reference
Sister chromatid exchange	Chinese hamster/bone marrow	+	Roszinsky-Kocher et al. 1979
DNA binding	Mouse skin	+	Weyand et al. 1987a
BENZO(k)FLUORANTHENE			
Mammalian systems: DNA binding	Mouse skin	+	Weyand et al. 1987
BENZO(ghi)PERYLENE			
Host-mediated systems: Transformation	Hamster embryos/ transplacental exposure	-	Quarles et al. 1979
BENZO(e)PYRENE			
Mammalian systems: Gene mutation	Mouse/dominant lethals	+	Epstein 1968; Generoso et al. 1982; Russell 1977
	Mouse/spot test	+	Davidson and Dawson 1976;1977
DNA damage DNA synthesis	Rat hepatocytes/unscheduled	-	Miralis et al. 1982
	Mouse germ cells/unscheduled DNA synthesis	-	Sega 1979
DNA binding	Mouse skin	+	Weyand et al. 1987a; Rice et al. 1984
Chromosome aberrations	Chinese hamster/bone marrow	+	Roszinsky-Kocher et al. 1979
	Chinese hamster/bone marrow	(+)	Bayer 1978
	Mouse/heritable translocation	-	Generoso et al. 1982
Sister chromatid exchange	Chinese hamster/bone marrow	+	Roszinsky-Kocher et al. 1979; Bayer 1978
Micronuclei	Mouse/bone marrow	+	Salamone et al. 1981
	Mouse/bone marrow	-	Bruce and Heddle 1979
	Chinese hamster/bone marrow	-	Bayer 1978
Sperm abnormalities	Mouse	+	Bruce and Heddle 1979; Topham 1980

TABLE 2-5 (Continued)

End Point	Species (Test System)	Results	Reference
Insect systems:			
Gene mutation	*D. melanogaster*/ sex-linked recessive	(+)	Vogel et al. 1983
	D. melanogaster/ sex-linked recessive	-	Zijlstra and Vogel 1984; Valencia and Houtchens 1981
	D. melanogaster/ somatic mutation	+	Fahmy and Fahmy 1980
Chromosome aberration	*D. melanogaster*	(+)	Vogel et al. 1983
Host-mediated systems:			
Gene mutation	*S. typhimurium*/ mouse host-mediated	-	Simmon et al. 1979; Glatt et al. 1985
	S. cerevisiae/ mouse host-mediated	-	Simmon et al. 1979
Sister chromatid exchange	Chinese hamster V79/ mouse host-mediated	+	Sirianni and Huang 1978
Transformation	Hamster embryos/ transplacental exposure	+	Quarles et al. 1979
	CHRYSENE		
Mammalian systems:			
Chromosome aberrations	Chinese hamster/bone marrow	-	Roszinsky-Kocher et al. 1979
Sister chromatid exchange	Chinese hamster/bone marrow	+	Roszinsky-Kocher et al. 1979
Host-mediated systems:			
Gene mutation	*S. typhimurium*/ mouse host-mediated	-	Simmon et al 1979
	S. cerevisiae/ mouse host-mediated	-	Simmon et al. 1979
	DIBENZ(a,h)ANTHRACENE		
Mammalian systems:			
Chromosome aberrations	Chinese hamster/bone marrow	-	Roszinsky-Kocher et al. 1979
Sister chromatid exchange	Chinese hamster/bone marrow	+	Roszinsky-Kocher et al. 1979

TABLE 2-5 (Continued)

End Point	Species (Test System)	Results	Reference
	FLUORANTHENE		
Mammalian systems: Sister chromatid exchange	Mouse/bone marrow	-	Palitti et al. 1986
	INDENO(1,2,3-c,d)PYRENE		
Mammalian systems: DNA binding	Mouse skin	+	Weyand et al. 1987
	PHENANTHRENE		
Mammalian systems: Chromosome aberrations	Chinese hamster/bone marrow	-	Roszinsky-Kocher et al. 1979; Bayer 1978
Sister chromatid exchange	Chinese hamster/bone marrow	+	Roszinsky-Kocher et al. 1979; Bayer 1978
Micronuclei	Chinese hamster/bone marrow	-	Bayer 1978
Host-mediated systems: Gene mutation	_S. typhimurium_/ mouse host-mediated	-	Simmon et al. 1979
	S. cerevisiae/ mouse host-mediated	-	Simmon et al. 1979
Transformation	Hamster embryos/ transplacental exposure	-	Quarles et al. 1979
	PYRENE		
Mammalian systems: Micronuclei	Mouse/bone marrow	-	Salamone et al. 1981
Insect systems: Gene mutation	_D. melanogaster_/ sex-linked recessive	-	Valencia and Houtchens 1981
Host-mediated systems Sister chromatid exchange	Chinese hamster V79/ mouse host-mediated	-	Sirianni and Huang 1978

- = negative result; + = positive result; (+) = equivocal or weakly positive result

* = A positive result was obtained in one experiment; this result was not reproduced in the same laboratory or in a second laboratory.

lymphoblasts in an *in vitro* test system with an exogenous metabolic activation system (Barfknecht et al. 1982); negative results were obtained in a second test without metabolic activation (Crespi et al. 1985; Rocchi et al. 1980). In test systems using non-human cells, positive results were reported for indeno(1,2,3-c,d)pyrene and mixed results were reported for benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(ghi)perylene, chrysene and fluoranthene (Table 2-4).

The majority of the test results for anthracene, phenanthrene and pyrene are negative, although positive results were reported for each chemical in at least one *in vitro* test, suggesting that they may have the potential to cause some genotoxic effects. There are, however, reports of these PAHs being mutagenic in *Salmonella typhimurium*, and positive results were obtained with these three chemicals in several *in vitro* mammalian cell systems (Table 2-4).

There is no evidence that acenapthene, acenaphthylene or fluorene are genotoxic. The results for these chemicals are consistently negative, but the genetic effects have been studied in only a few *in vitro* assays; they have not been tested *in vivo*. Thus, it is possible that further tests will reveal that these three chemicals possess genotoxic properties.

The results of the studies presented in Tables 2-4 and 2-5 indicate that several of the 15 PAHs discussed in this profile are genotoxic in both non-mammalian and mammalian systems. This, together with the observation that several of these chemicals also tested positive in *in vitro* human systems, suggests that PAHs have the potential to induce genotoxic effects in humans. Thus, it is possible that genotoxic effects may occur in humans exposed to PAHs.

Cancer. PAHs express their carcinogenic activity through biotransformation to chemically reactive intermediates which then covalently bind to cellular macromolecules (i.e., DNA) leading to mutation and tumor initiation. The products of PAH metabolism include epoxide intermediates, dihydrodiols, phenols, quinones and their various combinations (see Section 2.3.3, Metabolism). The bay-region (e.g. the sterically hindered, cup-shaped area between carbons-10 and 11 of benzo(a)pyrene or 1 and 12 of benz(a)anthracene) diol epoxide intermediates of PAHs are currently considered to be the ultimate carcinogen for alternant PAHs (Jerina et al. 1980). These diol epoxides are easily converted into carbonium ions which are alkylating agents and thus mutagens and initiators of carcinogenesis. However, several of the tumorigenic PAHs (i.e. the non-alternant PAHs) discussed in this profile do not have a bay-region, or have been shown not to be similarly activated via a bay-region epoxide (e.g. Amin et al. 1985a, 1985b). This has important implications regarding the expression of carcinogenicity for the non-alternant PAHs. If these chemicals are activated to carcinogens via a different mechanism than the alternant PAHs, then they may also differ with respect to tumor site and species specificity.

A prerequisite for conversion of PAHs into these active bay region diol epoxides is the presence of cytochrome P-450 and associated enzymes responsible for this conversion. These enzymes can be found primarily in the liver, but they are also present in the lung, intestinal mucosa and other tissues. Thus, factors such as distribution to the target tissue(s), solubility, and intracellular localization proximate to these enzymes figure prominently in the expression of a PAH's carcinogenicity.

Changes in the cytochrome P-450 system can affect the carcinogenicity of the PAHs. This system is susceptible to induction by the PAHs themselves as well as other chemicals commonly found in the environment. The degree and specificity (i.e., which enzymes are affected) of induction depends on the tissue and species and strain. The induction of one enzyme particularly important to the metabolism of PAHs, aryl hydrocarbon hydroxylase (AHH), is also known to be under genetic control (see discussions in Section 2.2.2 on responsive vs. non responsive mouse strains). Given the heterogeneity of human genotypes, it is likely that certain human subpopulations exist that are more susceptible to AHH induction, and thus more susceptible to the induction of cancer (see Section 2.8).

Once the reactive bay region epoxide is formed, it may covalently bind to DNA and other cellular macromolecules and presumably initiate mutagenesis and carcinogenesis. Indeed, the level of DNA-adduct formation has been found to correlate with tumor induction activity for a number of PAHs in newborn rat liver and lung (Weyand and LaVoie 1988). Undoubtedly several other factors yet to be determined are involved in the ultimate expression of PAH-induced carcinogenicity.

Although the bulk of this work on PAH-induced carcinogenicity has been done in animal models and animal in vitro systems, recent work in human in vitro systems indicates that these same mechanisms may be active in humans. For example, induction of AHH and formation of the reactive intermediate, benzo(a)pyrene 7,8-diol, has been observed in the epithelial tissue from human hair follicles (Merk et al. 1987). All the steps necessary for cellular transformation and cancer induction were demonstrated in cultured human skin fibroblasts: benzo(a)pyrene induced AHH activity, altered cellular proliferation kinetics and caused DNA damage (Milo et al. 1978). Thus, humans are most likely to also be susceptible to tumor induction by PAHs by these mechanism(s).

Evidence exists to indicate that certain PAHs are carcinogenic in humans. The evidence in humans comes primarily from occupational studies where workers involved in such processes as coke production, roofing, oil refining or coal gasification are exposed to mixtures containing PAHs (e.g., coal tar, roofing tar, soot, coke oven emissions, soot, crude oil). PAHs have not been clearly identified as the causative agent, however. Cancer associated with exposure to PAH-containing mixtures in humans occurs predominantly in the lung and skin following inhalation and dermal exposure, respectively. Some ingestion of PAHs is likely due to swallowing of particles containing PAHs subsequent to mucociliary clearance of these particulates from the lung.

Certain PAHs are carcinogenic to animals by the oral route (e.g., benz(a)anthracene, benzo(a)pyrene, and dibenz(a,h)anthracene). However, only a few of these compounds have been assayed by the oral route. The results of dermal studies indicate that benz(a)anthracene, benzo(a)pyrene, benzo(b)fluoranthene, benzo(k)fluoranthene, chrysene, dibenz(a,h)anthracene and indeno(1,2,3-cd)pyrene are tumorigenic in rats and mice following dermal exposure. The sensitivity of mouse skin towards PAH tumorigenesis forms the basis for the extensive studies performed using dermal administration. This tumorigenicity can be enhanced or modified with concomitant exposure to other PAHs, long straight chain hydrocarbons (i.e., dodecane) or similar organic compounds commonly found at hazardous waste sites. Thus, humans exposed to PAHs in combination with these substances could be at risk for developing skin cancer.

For many of the carcinogenic PAHs discussed in this profile, it would appear that the site of tumor induction is influenced by the route of administration, i.e., stomach tumors are observed following ingestion, lung tumors following inhalation, and skin tumors following dermal exposure. However, the observations (discussed below) that 1) mammary tumors are induced following intravenous injection in Sprague-Dawley rats, 2) a similar susceptibility to tumor development on rat skin as compared to that of mice after dermal application is not observed, and 3) oral cavity tumors are not observed when benzo(a)pyrene is administered in the diet suggest that the point of first contact may not always be the site of PAH-induced tumors. The results of carcinogenicity studies conducted with the 15 PAHs discussed in this profile by parenteral routes of exposure are summarized in Table 2-6.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental

TABLE 2-6. Summary of Carcinogenicity Studies with PAHs Using Parenteral Routes of Exposure

Chemical	Species	Route	Duration	Result/Site	Reference
Anthracene	Rat	Lung implantation	1 dose, 55-week observation	-	Stanton et al. 1972
Benz(a)anthracene	Mouse	Subcutaneous	Single dose	+/injection site sarcomas	Steiner and Falk 1951; Steiner and Edgecomb 1952
	Mouse	Subcutaneous	10 weeks	+/injection site	Boyland and Sims 1967
	Mouse	Intramuscular	--	+/fibrosarcomas, hemangio-endotheliomas	Klein 1952
	Mouse	Intravenous	1 dose, 13-week observation	+/injection site sarcomas	Shimkin and Stoner 1975
	Newborn mouse	Subcutaneous	--	+/lung, liver	Grover et al. 1975
	Newborn mouse	Intraperitoneal	3 days	+/lung	Levin et al. 1984
	Hamster	Intratracheal	30 weeks	-	Sellakumar and Shubik 1974
Benzo(a)pyrene	Mouse	Subcutaneous	Single dose	+/injection site sarcomas	Pfeiffer 1977
	Newborn mouse	Intraperitoneal	Single dose	+/liver	LaVoie et al. 1987
	Newborn mouse	Intraperitoneal	--	+/lung	Busby et al. 1984
	Rat	Intramammary	Single dose	+/mammary gland	Cavalieri et al. 1988b, 1988c
	Mouse	Intravaginal	5 months	+/cervix	Naslund et al. 1987
	Rat	Intrapulmonary	Single dose	+/lung	Deutsch-Wenzel et al. 1983
	Hamster	Intratracheal	Chronic	+/lung	Feron and Kruysse 1978
	Hamster	Intratracheal	Chronic	-	Kunstler 1983
	Rat	Tracheal implant	Intermediate	+/tracheal	Nettesheim et al. 1977
Benzo(b)fluoranthene	Newborn mouse	Intraperitoneal	Single dose	+/liver	LaVoie et al. 1987
	Rat	Intrapulmonary	Single dose	+/lung	Deutsch-Wenzel et al. 1983
	Hamster	Intratracheal	30 weeks	-	Sellakumar and Shubik 1974
Benzo(ghi)perylene	Mouse	Subcutaneous	Single dose	-	IARC 1983
	Rat	Intrapulmonary	Single dose	+	Duetch-Wenzel et al. 1983
Benzo(k)fluoranthene	Newborn mouse	Intraperitoneal	Single dose	-	LaVoie et al. 1987
	Rat	Intrapulmonary	Single dose	+/lung	Deutsch-Wenzel et al. 1983
Chrysene	Newborn mouse	Intraperitoneal	--	-	Buening et al. 1979a
	Newborn mouse	Intraperitoneal	Single dose, 70-week observation	+/liver	Grover et al. 1975
	Mouse	Subcutaneous	10 weeks	+/injection site tumors	Boyland and Sims 1967
Dibenz(a,h)anthracene	Newborn mouse	Intraperitoneal	--	+/lung	Buening et al. 1979b
	Mouse	Subcutaneous	Single dose, 9-month observation	+/fibrosarcomas	Lubet et al. 1983a
	Mouse	Subcutaneous	10 weeks	+/injection site tumors	Boyland and Sims 1967
	Hamster	Intratracheal	30 weeks	-	Sellakumar and Shubik 1974
Fluoranthene	Mouse	Intraperitoneal	15 days	+/lung	Busby et al. 1984

TABLE 2-6 (Continued)

Chemical	Species	Route	Duration	Result/Site	Reference
Fluorene	Mouse	Subcutaneous	Single dose	-	Roe 1962; Shear and Luter 1941; Steiner 1955
Indeno(1,2,3-cd)pyrene	Newborn mouse	Intraperitoneal	Single dose	-	LaVoie et al. 1987
	Mouse	Subcutaenous	3 months	+/injection site sarcomas	Lacassagne et al. 1963
	Rat	Intrapulmonary	Single dose	+/lung	Deutsch-Wenzel et al. 1983
Phenanthrene	Newborn mouse	Intraperitoneal	--	-	Buening et al. 1979a
	Mouse	Subcutaneous	Single dose	-	Grant and Roe 1963; Roe 1962; Shear and Luter 1941; Steiner 1955
Pyrene	Mouse	Subcutaneous	Single dose	-	Roe 1962; Shear and Luter 1941;
	Hamster	Intratracheal	30 weeks	-	Sellakumar and Shubik 1974

+ = increased incidence of tumors.
- = no increase in tumor incidence.

conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc and selenium). Biomarkers of exposure to PAHs are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by PAHs are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to PAHs

PAHs and their metabolites can be measured in the urine of exposed individuals. In workers exposed to PAHs and dermatology patients treated with coal tar, the PAH metabolite 1-hydroxypyrene has been detected in the urine at concentrations of 0-40 μg/g creatinine or 290 ng/g creatinine, respectively (Jongeneelen et al. 1985). The amount of 1-hydroxypyrene detected in urine samples taken during the weekend was less than that detected during the weekdays, when the exposure was presumably higher than on the weekends. No correlation was found between occupational exposure levels and urine levels, so it is not known whether urine metabolites could be detected following exposure to low levels of PAHs (as might be expected to occur in individuals living in the vicinity of hazardous waste sites). The identification of PAH metabolites in the urine could serve as a method of biological monitoring of exposed workers, and possibly individuals living in the vicinity of hazardous waste sites where PAHs have been detected following both short- and long-term exposure. In addition, autopsies performed on cancer-free patients found PAH levels of 11 to 2,700 ppt in fat samples. Several PAHs were detected, including anthracene, pyrene, benzo(e)pyrene, benzo(k)fluoranthene, benzo(a)pyrene, and benzo(ghi)perylene, with pyrene being detected in the highest concentrations (Obana et al. 1981). A similar study done on livers from cancer-free patients found levels of 6-500 ppt of all of the same PAHs except benzo(e)pyrene, which was not detected in the liver. As in the fat samples studies, pyrene appeared in the highest concentrations in the liver, but the overall levels were less than in fat (Obana et al. 1981). However, because of the ubiquitous nature of PAHs in the environment, detection of PAH metabolites in the body tissues or fluids is not specific for exposure to PAHs from hazardous waste sites. In addition, it is impossible to determine from these biological media whether exposure was to high or low levels of PAHs or if the exposure duration was short- or long-term.

PAHs form DNA adducts that can be measured in body tissues or blood following exposure to PAHs or compounds containing PAHs. Again, these PAH-DNA adducts are not specific for any particular source of PAHs, and the adducts measured could have been from exposure to other sources of PAHs, such as complex mixtures that contain PAHs (e.g., crude oils, various high-boiling point distillates, complex petroleum products, coal tars, creosote, and the products of coal liquification processes), as well as vehicle exhausts, wild fires, agricultural burning, tobacco smoke, smoke from home heating of wood, cereals, grains, flour, bread, vegetables, fruits, meat, processed or pickled foods, beverages, and grilled meats. Again, it is impossible to determine from these adducts whether exposure was to high or low levels of PAHs or if the exposure duration was short- or long-term.

2.5.2 Biomarkers Used to Characterize Effects Caused by PAHs

The available genotoxicity data indicate that several of the 15 PAHs discussed in this profile are genotoxic in both nonmammalian and mammalian systems and are indirect mutagens (i.e., requiring the presence of an exogenous mammalian metabolic system). There were no tests reported for humans exposed to benzo(a)pyrene (the most widely tested PAH) in vivo, but several types of cultured human tissue cells demonstrated positive results for benzo(a)pyrene-induced genotoxicity (as evidenced by the induction of chromosomal aberrations, sister chromatid exchange) and binding of benzo(a)pyrene to DNA. Thus, although these results are exclusively from in vitro tests and the limited genotoxicity tests conducted on urine obtained from humans exposed to creosote (a complex mixture containing PAHs) have been negative, these genotoxic effects observed in human tissue cells may serve as a biomarker of effects for at least one of the PAHs, benzo(a)pyrene. PAHs have been shown to cause noncancer adverse effects on rapidly proliferating tissues such as the hematopoietic system, the lymphoid system, and the skin in both humans and animals. Myelosuppression, consisting of cumulative leukopenia and thrombocytopenia was observed in cancer patients undergoing chemotherapy with anthracene-containing therapeutic agents. The skin is susceptible to PAH-induced toxicity in both humans and animals. Regressive verrucae were reported following subchronic application of benzo(a)pyrene to human skin. Although reversible and apparently benign, these changes were thought to represent neoplastic proliferation. Benzo(a)pyrene application also apparently exacerbated skin lesions in patients with pre-existing skin conditions (pemphigus vulgaris and xeroderma pigmentosum). Workers exposed to substances that contain PAHs (e.g., coal tar) experienced chronic dermatitis and hyperkeratosis (EPA 1988a). However, none of these end points are specific to PAHs, and all can be seen with other agents. No other biomarkers (specific or otherwise) have been identified following exposure to PAHs.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Because humans are usually exposed to PAHs in complex mixtures rather than as individual PAHs, it is important to understand the potential interactions between the PAHs and other components of the mixture. Synergistic and/or antagonistic interactions with regard to the development of health effects, particularly carcinogenesis, may occur.

The extent of human exposures to PAH mixtures in occupational settings is generally not known in quantitative terms. However, exposures to complex chemical mixtures that include PAHs, such as use of tobacco products and exposure to roofing tar emissions, coke oven emissions, coal tar and shale oils, have been associated with adverse health effects in humans. The biological consequences of human exposure to complex mixtures of PAHs depend on the interaction of the various strongly carcinogenic, weakly carcinogenic, or noncarcinogenic PAHs. For example, there is evidence to suggest that PAHs in cigarette smoke require other components in the smoke in order to exert their tumorigenic effect (Akin et al. 1976).

The interaction between noncarcinogenic and carcinogenic PAHs has been extensively examined in animals. Noncarcinogenic PAHs exhibit cocarcinogenic potential and tumor-initiating and promoting activity when applied with benzo(a)pyrene to the skin of mice. Weakly carcinogenic or noncarcinogenic PAHs including benzo(e)pyrene, benzo(ghi)perylene, fluoranthene or pyrene significantly elevated the tumor incidence of benzo(a)pyrene. Benzo(e)pyrene, fluoranthene and pyrene were more potent cocarcinogens than benzo(ghi)perylene (Van Duuren and Goldschmidt 1976; Van Duuren et al. 1973). Benzo(e)pyrene, fluoranthene and pyrene have also demonstrated weak tumor promoting activity following initiation with benzo(a)pyrene, and these compounds increased benzo(a)pyrene-DNA adduct formation (Rice et al. 1984; Slaga et al. 1979; Smolarek et al. 1987; Van Duuren and Goldschmidt 1976; Van Duuren et al. 1973).

Interactions between selected noncarcinogenic PAHs and carcinogenic benzo(a)pyrene have also been documented to reduce the carcinogenic potential of benzo(a)pyrene in animals. Benzo(a)fluoranthene, benzo(k)fluoranthene, chrysene, perylene and a mixture of anthracene, phenanthracene and pyrene significantly inhibited benzo(a)pyrene-induced injection site sarcomas. However, other PAHs including anthracene, benzo(ghi)perylene, fluorene, and indeno(1,2,3-cd)pyrene had no antagonistic effects (Falk et al. 1964). Phenanthracene administration with benzo(a)pyrene decreased the DNA adduct formation in mice (Rice et al. 1984).

There is evidence to suggest that benz(a)anthracene serves as an anticarcinogen when administered with benzo(a)pyrene. Coadministration of benz(a)anthracene and benzo(a)pyrene decreased benzo(a)pyrene metabolism, benzo(a)pyrene-DNA adduct formation, and reduced the mutation activity of benzo(a)pyrene on hamster embryo cells. It has been postulated that the anticarcinogenic activity of benz(a)anthracene results from competition with benzo(a)pyrene for mixed function oxidase (MFO) enzymes, rather than the induction of detoxifying enzymes (Smolarek et al. 1986).

The synergistic effect of individual PAHs on the mutagenicity of benzo(a)pyrene have also been demonstrated. Anthracene and benzo(e)pyrene enhanced the mutagenicity of benzo(a)pyrene, the maximal increase being obtained with anthracene.

Benzo(a)pyrene and dibenz(a,h)anthracene in combination with 10 noncarcinogenic PAHs were less potent tumor-inducers than was dibenz(a,h)anthracene alone or in combination with benzo(a)pyrene. The noncarcinogenic PAHs include benzo(e)pyrene, benz(a)anthracene, phenanthrene, anthracene, pyrene, fluoranthene, chrysene, perylene, benzo(ghi)pyrene, and coronene. Dose-response relationships for tumor incidences were observed for benzo(a)pyrene, dibenz(a,h)anthracene either alone and in combination with the 10 noncarcinogenic PAHs; however, no treatment-related sarcoma incidences were observed for any of the 10 noncarcinogenic PAHs (Pfeiffer 1977).

Phenanthrene, a noncarcinogenic PAH, demonstrated a dose-related inhibition on dibenz(a,h)anthracene-induced carcinogenicity in mice. Phenanthrene significantly reduced the incidence of injection site sarcomas elicited by dibenz(a,h)anthracene, especially at low doses. However when triethylene glycol was the vehicle administered in combination with phenanthrene and dibenz(a,h)anthracene, a substantial increase (50%) in the rate of tumor induction was observed (Falk et al. 1964).

Several experiments have shown that most PAH mixtures are considerably less potent than individual PAHs. Various combustion emissions and benzo(a)pyrene have been examined for carcinogenic potency and tumor initiation activity on mouse skin. In all cases, PAH mixtures were much less potent than benzo(a)pyrene. The authors calculated relative potency estimates that ranged from 0.007 for coke oven emissions extract to less than 0.002 for diesel engine exhaust extract, using papillomas per mouse per milligram as the end point (Slaga et al. 1980b). Another study demonstrated that the relative tumorigenicity of automobile exhaust condensate (AEC), diesel emission condensate, and a representative mixture of carcinogenic PAHs were 0.0053, 0.00011 and 0.36, respectively, in comparison to benzo(a)pyrene following chronic application to mouse skin (Misfeld 1980). AEC has also exhibited an antagonistic influence on benzo(a)pyrene carcinogenicity when subcutaneously administered to mice; this effect was particularly augmented at higher benzo(a)pyrene concentrations (Pott et al. 1977).

Predicting the toxicity of a complex mixture on the basis of one of several of its components may be misleading, due to the interactions among the components that may modify toxicity. Since PAHs require metabolic activation by monoxygenases to elicit carcinogenic effects, any alteration in these metabolic pathways will influence the observed toxicity. There are two primary mechanisms by which chemicals interact with PAHs to influence toxicity. A compound may compete for the same metabolic activating enzymes and thereby reduce the toxicity of carcinogenic PAHs or it may induce the metabolizing enzyme levels to result in a more rapid detoxification of the carcinogenic PAHs (Levin et al. 1976). Many monoxygenase inducers are ubiquitous in the environment and they may act synergistically with PAHs. For example, environmental contaminants such as TCDD, polychlorinated biphenyls (PCB) and 3,3',4,4'-tetrachlorobiphenyl (TCBP) can increase microsomal enzyme activity and consequently affect PAH toxicity (Jacob et al. 1987; Kouri et al. 1978). Interactions can thus play important modulatory roles in the expression of PAH toxicity that may not be adequately reflected based on the toxicity of a single PAH.

The majority of human exposures to PAHs occur in the presence of particles, which affect the pharmacokinetics and carcinogenicity of PAHs. Coadministration of benzo(a)pyrene and particulate material, such as hematite (Fe_2O_3) and arsenic trioxide (As_2O_3) greatly increases respiratory tract tumor yields in experimental animals following intratracheal instillation, probably by a synergistic effect (Pershagen et al. 1984; Saffiotti et al. 1972; Stenback et al. 1976; Stenback and Rowland 1979). The effects of particles on the potential human carcinogenicity of PAHs is likely to be similar. When benzo(a)pyrene is particle-bound clearance from hamster lungs is slower than that of pure benzo(a)pyrene aerosol, increasing the length of time the lungs were exposed and increasing the dose to the gastrointestinal tract as a result of mucociliary clearance. Respirable benzo(a)pyrene-containing particulates such as diesel exhaust, when coated with the phospholipid component of a pulmonary surfactant, are genotoxic (Wallace et al. 1987). Dusts can increase the rates of pulmonary cell proliferation (Harris et al. 1971; Stenback et al. 1976; Stenback and Rowland 1979), which in turn increases the cells' susceptibility to an initiation event in the presence of a carcinogen.

Asbestos also exerts a synergistic influence on cigarette smoke (which contains several PAHs) in the development of bronchopulmonary cancers. This has important implications for workers occupationally exposed to asbestos, who also smoke. The interaction between PAH and asbestos may be explained partly by differences in the kinetics of PAH cell uptake when PAH is preadsorbed on asbestos (Fournier and Pezerat 1986). Plutonium oxide (PuO_2) has also been shown to enhance benzo(a)pyrene-induced lung carcinogenesis following simultaneous inhalation of both compounds (Metivier et al. 1984).

Naturally occurring compounds have been found to induce the enzymes that metabolize PAHs leading to either increased or decreased toxicity. Compounds which exert a protective effect against the carcinogenicity of PAHs via this mechanism include plant flavonoids, plant phenols, antioxidants, retinoids (vitamin A), garlic oil, selenium, and Chinese herbs. Plant flavonoids can induce microsomal monooxygenases and reduce the carcinogenicity of benzo(a)pyrene (Weibel 1980). Flavones administered orally or dermally increased benzo(a)pyrene hydroxylase activity in the small intestine and skin, respectively and prevented pulmonary adenoma formation and skin tumors initiated by benzo(a)pyrene (Rahimtula et al. 1977).

Dietary plant phenols, such as tannic acid, quercetin, myricetin and anthraflavic acid exhibit a protective effect against the tumorigenicity of benzo(a)pyrene and other PAHs by altering the metabolic pathways which detoxify and activate PAHs to their ultimate carcinogenic metabolites, thus suppressing PAH metabolism and subsequent PAH-DNA adduct formation. It has been suggested that the possible mechanism for the anticarcinogencic effect of these plant phenols may be an inhibitory effect on the binding of the ultimate carcinogen to the target tissue DNA (Mukhtar et al. 1988). Antioxidants also affect benzo(a)pyrene hydoxylation by rat liver microsomal MFOs, and reduce the bacterial mutagenicity of benzo(a)pyrene in the presence of rat liver microsomes and cofactors (Rahimtula et al. 1977). Antioxidants such as BHA, BHT, phenothiazine, phenothiazine methosulfate and ethoxyquin all can reduce the quantitative yield of benzo(a)pyrene metabolites in incubations with rat liver microsomes (Sullivan et al. 1978).

Retinoids, of which vitamin A is a member, have demonstrated an antagonistic effect on benzo(a)pyrene-induced carcinogenicity. Vitamin A has been shown to prevent and/or reverse the genetic damage caused by benzo(a)pyrene. Although the protective mechanism has not been fully elucidated, it has been suggested that vitamin A interferes with the activation of benzo(a)pyrene to its reactive metabolites, thus reducing the amount of benzo(a)pyrene-DNA binding in rat liver and target tissues (i.e., stomach) to prevent the mutagenic action of benzo(a)pyrene. It has also been suggested that vitamin A can also enhance DNA repair (McCarthy et al. 1987; Rao et al. 1986). Conversely, vitamin A deficiency enhances the mutagenicity and carcinogenic effect of cigarette smoke and benzo(a)pyrene. This activity is related to a decreased level of free radical scavengers like ascorbic acid and glutathione in the liver (Alzieu et al. 1987). Another study observed that vitamin A deficient animals exposed to cigarette smoke via inhalation exhibited enhanced benzo(a)pyrene-DNA adduct formation (Gupta et al. 1987). This has important implications for humans who smoke and consume diets deficient in vitamin A.

Garlic oil also exhibits an antagonistic effect on benzo(a)pyrene by inhibiting benzo(a)pyrene-induced skin carcinogenesis in Swiss mice during the initiation phase (Sadhana et al. 1988). A primary constituent of garlic oil, allyl methyl trisulfide (ATM), has also demonstrated an inhibitory effect on benzo(a)pyrene induced neoplasia of the forestomach in mice (Sparnins et al. 1986).

Selenium has been shown to reduce the mutagenicity of benzo(a)pyrene as well as aryl hydrocarbon hydroxylase activity (AHH). Chinese herbs commonly used in anti-cancer drugs have also been demonstrated to inhibit the mutagenicity of benzo(a)pyrene (Lee and Lin 1988).

The ubiquitous nature of PAHs in the environment, particularly as constituents of complex mixtures such as automobile emissions, coal tar, coke oven emissions and combustion products of tobacco, increases the likelihood that the type of interactions discussed will occur. Thus, interactions may play a decisive role in the expression of toxicity and the development of cancer in exposed populations.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Data indicate that specific subsections of the population may be susceptible to the toxic effects produced by exposure to PAHs. These subsections include the unborn and people with numerous conditions such as genetically inducibility aryl hydrocarbon hydroxylase (AHH) activity, nutritional deficiencies, genetic diseases that influence the efficiency of DNA-repair, and immunodeficiency due to age or disease. Other subsections of the population that may be susceptible to the toxic effects of PAHs are people who smoke; those with a history of excessive sun exposure; people with liver and skin diseases; and women, especially of child-bearing age. Data also indicate that the population in general may be at increased risk of developing lung cancer following prolonged inhalation of PAH-contaminated air and skin cancer following concurrent dermal exposure to PAHs and sunlight. There is some limited evidence that indicates all people could be sensitive at some point to the toxic effects of environmental contaminants, such as PAHs, due to stress and/or circadian rhythms.

Pre- and post-natal exposure to PAHs could produce adverse reproductive and developmental effects. Most PAHs and their metabolites cross the placenta because of their lipid solubility (Calabrese 1978; Shendrikova and Aleksandrov 1974). The unborn are susceptible to the toxic effects produced by maternal exposure to PAHs, such as benzo(a)pyrene because of an increased permeability of the embryonic and fetal blood-brain barrier and a decreased liver-enzyme conjugating function (Calabrese 1978, Shendrikova and Aleksandrov 1974). Due to PAH exposure greater incidences of embryo- and fetolethality, stillborns, resorptions, and malformations of the kidney and bladder have been observed in animals (Legraverend et al. 1984; Sheveleva 1978; Urso and Gengozian 1980, Urso and Johnson 1987). Delayed effects have been observed in the progeny of mothers exposed to PAHs, such as benzo(a)pyrene (Urso and Gengozian 1980). These delayed effects include sterility of progeny, immune suppression, and cancer in rodents (Legraverend et al. 1984, Mackenzie and Angevine 1981). Tobacco smoke contains both PAHs and particulate matter. These could interact synergistically in pregnant women who smoke to produce decreased birth weight, increased perinatal morbidity and mortality, and other diseases of the newborn (NRC 1983). PAHs in cigarette smoke, such as benzo(a)pyrene, have been associated with the induction of AHH activity in human placental tissue and a decrease in placental size (NRC 1983).

People with the genetic ability to induce aryl hydrocarbon hydroxylase (AHH) activity may also be susceptible to the possible carcinogenic effect of exposure to PAHs. This enzyme is a mixed-function oxidase that is involved in the metabolism of PAHs to certain reactive intermediates which can cause cell transformation, mutagenicity, and cytotoxicity. The incidence of this inducible genetic trait is low in 53%, intermediate in 37%, and high in 10% of the white population in the United States (Calabrese 1978). It has been proposed that genetically-expressed AHH inducibility is related to the development of bronchogenic carcinoma in persons exposed to PAHs contained in tobacco smoke. However, on the other hand, individuals with a greater ability to induce AHH may be able to rapidly detoxify PAHs and eliminate them, thus making them less susceptible to the toxic effects of PAHs. Approximately 45% of the general population are considered to be at high risk and 9% of the 45% are considered to be at very high risk of developing bronchogenic carcinoma following exposure to PAHs (Calabrese 1978). These percentages were estimated from the population frequency of genetically-controlled AHH induction (Calabrese 1978).

Certain nutritional deficiencies have been associated with an increased cancer incidence in PAH-exposed animals. These include deficiencies in vitamins A and C, iron, and riboflavin (Calabrese 1978). It is estimated that at least 25% of children between the ages of 7 and 12 and children of low income families consume less than the recommended dietary allowance (RDA) of vitamin A. It has also been estimated that between 10% and 30% of the infants, children, and adults of low income groups consume less than the RDA for vitamin C, 98% of all children consume less than the RDA for iron, and 30% of women and 10% of men between the ages of 30 and 60 years consume less than two-thirds of the RDA for riboflavin (Calabrese 1978). Other nutrients such as vitamin D, selenium, and protein can also influence the cancer incidence in animals exposed to PAHs (NRC 1983, Prasanna et al. 1987). Several studies have been conducted that investigated the interaction between nutrition and PAH exposure by administering benzo(a)pyrene to experimental animals. These nutritional factors either reduced the amount of benzo(a)pyrene binding to DNA in rat liver or stomach tissue (McCarthy et al. 1987), prevented or reversed genetic damage (Rao et al. 1986), or reduced the activity of AHH (Prasanna et al. 1987). It has also been observed that fasted rats showed increased toxicity due to benz(a)anthracene and chrysene exposure. This increased toxicity included reduced hepatic clearance due to decreased AHH activity and the acceleration of the depletion of cytochrome P-450 and other microsomal enzymes required to metabolize PAHs (Fiume et al. 1983).

People exposed to PAHs in conjunction with particulates from tobacco smoke, fossil-fuel combustion, coal fly ash, and asbestos fibers are at increased risk of developing toxic effects, primarily cancer. Even people not susceptible to the toxic effects of PAHs may become affected when exposure occurs in conjunction with exposure to particulates (NRC 1983). This synergistic action results from the adsorption of PAHs onto the particulates. They are transported more efficiently through membranes, cleared from tissue more slowly, and are distributed differently in tissues depending on the size and type of particulate matter. This increased PAH uptake results in more efficient induction of AHH activity at low PAH concentrations. This activity also increases the dose to the gastrointestinal tract due to mucociliary clearance (NRC 1983). This synergistic action between PAHs and particulate matter in air pollution has been associated with the occurrence of stomach cancer in humans (Fraumeni 1975).

Exposure to mixtures of PAHs may also increase the susceptibility of certain persons to the development of cancer. Tobacco smoke and air pollution contain mixtures of PAHs. Some PAHs, for example benzo(e)pyrene, increased the skin tumor initiating activity and the DNA-binding ability of benzo(a)pyrene (Slaga et al. 1979; Smolarek et al. 1987). Tobacco smoke (IARC 1983) and air pollution also contain many different PAHs, some that individually are thought to be non-carcinogenic, such as benzo(e)pyrene, benzo(ghi)perylene, fluoranthene, and pyrene, that can enhance the carcinogenic ability of benzo(a)pyrene (Van Duuren and Goldschmidt 1976; Van Duuren et al. 1973). It was determined that an extract from the products of diesel engine combustion was genotoxic if coated with a phospholipid component of a pulmonary surfactant (Wallace et al. 1987). Concurrent exposure of rats to sulfur dioxide and benzo(a)pyrene has been associated with an increased incidence of pulmonary squamous cell carcinomas as compared to rats exposed only to benzo(a)pyrene (Laskin et al. 1970). Exposure to dust, a common particulate, can increase the rate of pulmonary cell proliferation (Harris et al. 1971; Stenback and Rowland 1979; Stenback et al. 1976), which in turn increases the susceptibility of pulmonary cells to an initiation event in the presence of a carcinogen, such as benzo(a)pyrene.

Immunocompetence is an important factor in decreasing susceptibility of toxicity and disease due to exposure to environmental contaminants. Small children have an immature immune system while aging people may have a deficient immune system due to age, genetic factors, or disease. It has been demonstrated that some of the PAHs depress the immune system and can therefore be considered as possible cofactors in the development of lymphoreticular cancers (Calabrese 1978; NRC 1983). Some genetic diseases that may predispose a person to immune deficiency include ataxia telangiectasia, Wiskott-Aldrich syndrome, Bloom's syndrome, common variable immunodeficiency, selective IgA deficiency, Bruton's agammaglobulinemia, severe combined immunodeficiency, selective IgM deficiency, AIDS, and immunodeficiency with normal or increased immunoglobulins (NRC 1983). Immunological effects, such as allergic contact hypersensitivity which was antigen specific was produced in mice exposed to PAHs (Klemme et al. 1987).

Genetic diseases that reduce DNA-repair capabilities also increase an individual's susceptibility to PAH-related malignancy by reducing the efficiency of DNA repair. Some of the diseases seen are associated with an abnormality of the immune system (NRC 1983). Diseases that may be associated with DNA-repair deficiencies are classical and variant xeroderma pigmentosum, ataxia telangiectasia, Bloom's syndrome, Fanconi's anemia, familial retinoblastoma, D-deletion retinoblastoma, Progeria (Hutchinson-Gilford) syndrome, Down's syndrome, Dyskeratosis congenita, Cockayne's syndrome, Actinia keratosis, and cutaneous malignant melanoma (NRC 1983).

Women, especially of child-bearing age, may be at increased risk of reproductive dysfunction due to exposure to PAHs. Data from animal studies indicate the oocyte and follicle destruction occurs following dosing with PAHs (Urso and Gengozian 1980; Urso and Johnson 1987). Benzo(a)pyrene exposure may reduce fertility and the ability to bear children (Mackenzie and Angevine 1981; Rigdon and Rennels 1964). Exposure may also reduce fertility by ovarian dysfunction of exposed women (Swartz and Mattison 1985).

Subsections of the population that suffer from liver and skin diseases may be at increased risk of developing adverse effects due to PAH exposure. People suffering from severe liver dysfunction, due to either disease or a genetic deficiency that interferes with the ability to metabolize PAHs, can be at increased risk of premature death due to the development of immune deficiency caused by bone marrow depression leading to hemorrhage or infection (Robinson et al. 1975; Schnizlein et al. 1987). Exposure to PAHs could increase hepatic toxicity by inducing enzyme alterations, preneoplastic changes in hepatocytes referred to as gamma-GT foci, hepatic regeneration, and increased hepatic weight (Gershbein 1975; Nousiainen et al. 1984; Robinson et al. 1975; Torronen et al. 1981; Tsuda and Farber 1980; White and White 1939, Wilson et al. 1947). People with pre-existing skin conditions, such as pemphigus vulgaris and xeroderma pigmentosum, and those with normal skin may be at increased risk of developing adverse dermal effects ranging from rashes to cancer following exposure to some PAHs, such as benzo(a)pyrene, anthracene, benz(a)anthracene, pyrene (Bingham and Falk 1969; Cavalieri et al. 1977; Cavalieri et al. 1988b; Cottini and Mazzone 1939; Forbes et al. 1976; Habs et al. 1980; Klar 1938; Rhoads et al. 1954; Shubik and Porta 1957). Exposure to more than one PAH may enhance tumor development (Goldschmidt et al. 1973; Slaga et al. 1979; Van Duuren and Goldschmidt 1976; Van Duuren et al. 1973). Skin cancer induction has been associated with exposure to benz(a)anthracene, benoz(a)pyrene, benzo(b)fluoranthene, benzo(k)fluoranthene, chrysene, dibenz(a,h)anthracene, and indeno(1,2,3-cd)pyrene.

People with significant exposure to ultraviolet (UV) radiation, such as from sunlight may also be at increased risk of developing skin cancer due to PAH exposure. UV radiation has demonstrated a synergistic influence on PAH-induced skin cancer following dermal exposure. It enhances benzo(a)pyrene-induced skin carcinogenesis in the mouse, which is dependent on the dose of benzo(a)pyrene (Gensler 1988). Combined exposure to anthracene and sunlight could produce mutagenic lesions (Blackburn and Taussig 1975; Forbes et al. 1976). Experimental animals exposed concurrently to chronic UV irradiation and to PAHs were at a higher risk of skin tumor induction (Mukhtar et al. 1986).

Limited evidence indicates that all people could be sensitive to the toxic effects produced by PAH exposure during some periods of their lives due to stress and changes in the body's circadian rhythms (Calabrese 1978; NRC 1983).

2.8 ADEQUACY OF THE DATABASE

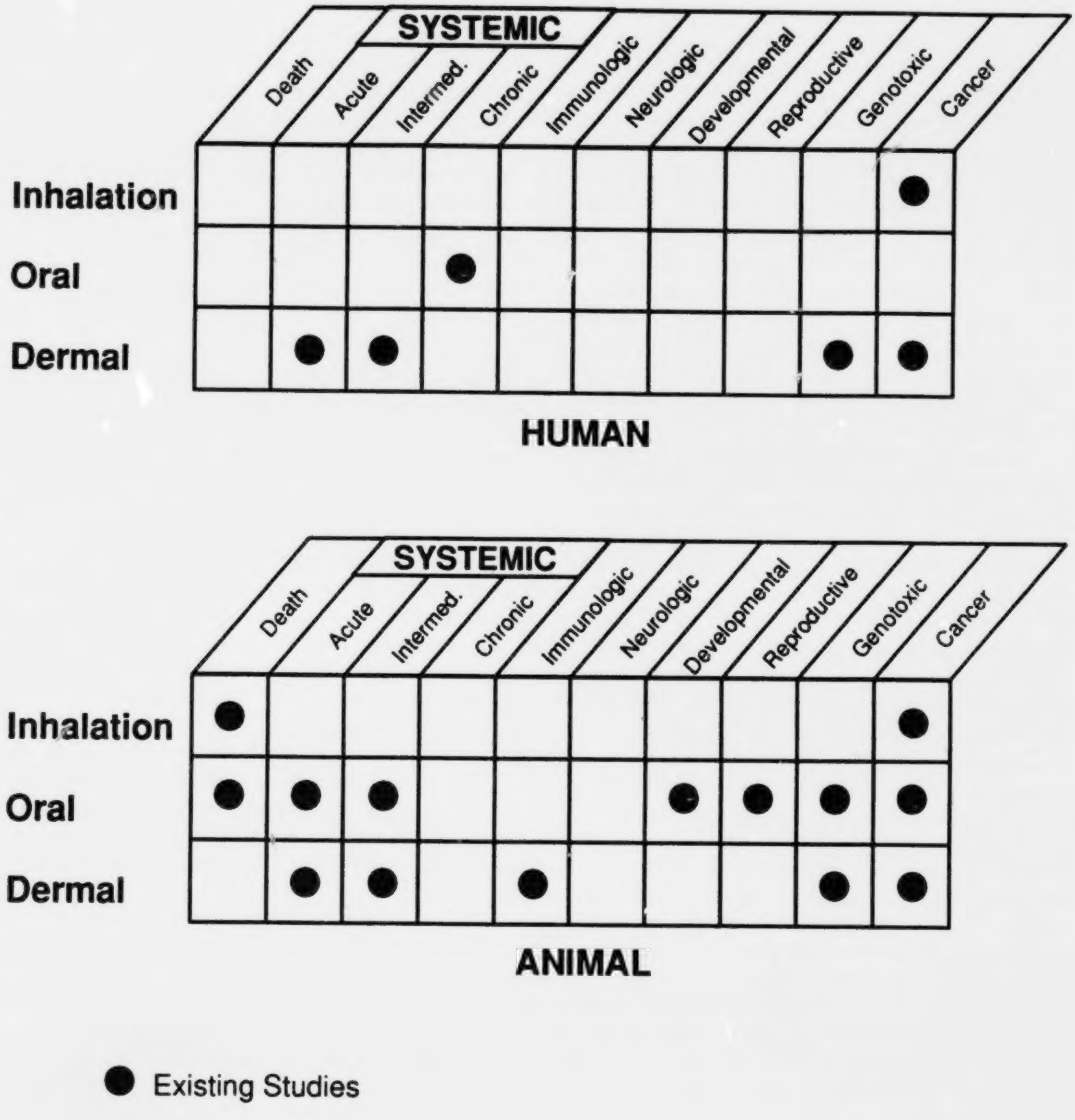
Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of PAHs is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of PAHs.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.8.1 Existing Information on Health Effects of Polycyclic Aromatic Hydrocarbons

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to PAHs are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of PAHs. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

The vast majority of literature reviewed concerning the health effects of PAHs in humans described case reports and longer-term studies in workers linking the occurrence of lung and skin cancer and adverse noncancer skin effects with exposure to PAH-containing mixtures such as coke-oven emissions, roofing-tar emissions, shale oils, and soot, and exposure to cigarette smoke. The predominant routes of exposure in the studies are inhalation and dermal, but the possibility of some degree of oral exposure cannot be ruled out. Due to lack of quantitative exposure information and the presence of other potentially carcinogenic substances in these mixtures, it is impossible to evaluate the contribution of an individual PAH to the effects observed.



		SYSTEMIC								
	Death	Acute	Intermed.	Chronic	Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
Inhalation										●
Oral				●						
Dermal		●	●						●	●

HUMAN

		SYSTEMIC								
	Death	Acute	Intermed.	Chronic	Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
Inhalation	●									●
Oral	●	●	●				●	●	●	●
Dermal		●	●		●				●	●

ANIMAL

● Existing Studies

FIGURE 2-5. Existing Information on Health Effects of PAHs

The database for the health effects of PAHs in experimental animals consists primarily of older animal studies that would be considered inadequate by current standards, and two-stage dermal carcinogenesis studies. As can be seen in Figure 2-5, very little information is available on the effects of inhalation exposure to PAHs in animals. However, oral and dermal exposures to PAHs have been shown in numerous studies to induce skin, lung, and forestomach tumors in animals, and noncancer adverse effects in rapidly proliferating tissues such as bone marrow, lymphoid organs, gonads, and intestinal epithelium. Benzo(a)pyrene is by far the most extensively studied of the PAHs; therefore the adverse effects of other less studied PAHs must generally be inferred from the results obtained with benzo(a)pyrene. This may over- or underestimate the health risk associated with the various PAHs.

2.8.2 Identification of Data Needs

Acute-Duration Exposure. Information is available on the effects of acute-duration exposures to PAHs in animals (oral and dermal). The types of information available includes acute hepatic and dermal toxicity data in animals. Little is known regarding the adverse health effects associated with acute-duration inhalation exposure to any of the PAHs in either humans or animals. The available information is sufficient to derive an acute oral MRL of 0.1 mg/kg/day for PAHs based on decreased weight of pups born to rats exposed to benzo(a)pyrene during pregnancy. However, available information is insufficient to derive an acute inhalation MRL. Identification of target organs (including effects on the liver and skin) from short-term animal studies following inhalation, oral, and dermal exposures would be useful in assessing the risk associated with the acute inhalation, ingestion, or skin contact by humans of PAH-contaminated air, water, or soils. This information would be useful to assess the risk to humans living in areas surrounding hazardous waste sites, since inhalation may be the primary exposure route at these sites. Furthermore, additional information on the acute effects of all of the PAHs in humans or animals following exposure by the oral and dermal routes would be helpful to assess the health risk associated with acute-duration exposure to the less well-studied PAHs via ingestion of or contact with contaminated, water or soils. This is particularly important for PAHs other than benzo(a)pyrene since nonalternant PAHs may exert different toxicities than alternant PAHs such as benzo(a)pyrene. The pharmacokinetic data on PAHs are insufficient to determine whether similar effects may be expected to occur across different routes of exposure.

Intermediate-Duration Exposure. Information is available on the effects of intermediate-duration exposures to some of the PAHs in humans (dermal) and in animals (oral and dermal). The exact duration and level of exposure in the human studies generally cannot be quantitated because the information is derived from anecdotal case reports that are flawed by confounding factors rather than controlled epidemiological studies. Animal studies with some of the PAHs describe predominantly dermal, hepatic, and hemolymphatic end points. The available information is insufficient to derive either an intermediate oral or inhalation MRL for PAHs because no intermediate-duration animal studies exist that describe effects other than increased liver weight and aplastic anemia (a serious effect). Little is known regarding the adverse health effects associated with intermediate-duration inhalation exposure to any of the PAHs in either humans or animals. This information would be useful to assess the risk to humans living in areas surrounding hazardous waste sites, since inhalation may be the primary exposure route at these sites. More information on the systemic effects (including effects on the liver, skin, and hemolymphatic system) of all of the PAHs in humans or animals following exposure by the oral and dermal routes would be helpful to assess the health risk associated with intermediate-duration exposure to the less-well-studied PAHs via ingestion of or contact with contaminated water or soils. This is particularly important for those PAHS other than benzo(a)pyrene since nonalternant PAHs may exert different toxicities than alternant PAHs such as benzo(a)pyrene. The pharmacokinetic data on PAHs are insufficient to determine whether similar effects may be expected to occur across different routes of exposure.

Chronic-Duration Exposure and Cancer. Few controlled epidemiological studies have been conducted in humans on the effects of exposure to PAHs or PAH-containing mixtures because they would be difficult to conduct due to the presence of too many confounding factors. However, information is available on the effects of chronic-duration dermal exposures to PAH-containing mixtures in humans. The exact duration and level of exposure in the human studies generally cannot be quantified because the information is usually derived from anecdotal case reports rather than controlled epidemiological studies. Epidemiological studies of workers in occupations where exposure to PAH-containing mixtures is common (e.g., coke production) would be useful to more fully assess the risk of inhalation and dermal exposure to PAHs, but they would be difficult to conduct. Several ingestion, intratracheal installation and skin-painting studies have been conducted in animals using various PAHs. Though many of these studies would be considered inadequate by current standards, the results nevertheless provide qualitative evidence that some of the PAHs can cause adverse noncancer effects on hemolymphatic elements. The available information is insufficient to derive either a chronic oral or inhalation MRL for PAHs because no adequate chronic-duration animal studies exist. Chronic studies by both the inhalation and oral routes of those PAHs found most often at hazardous waste sites and for which reliable data do not currently exist are needed to identify potential target organs given the potential for exposure by this route via ingestion of contaminated air, water, and soils. The pharmacokinetic data on PAHs are insufficient to determine whether similar effects may be expected to occur across different routes of exposure.

A large database on carcinogenicity exists on complex mixtures that contain PAHs (such as crude oils, various high boiling point distillates, complex petroleum products, coal tars, creosote, and the products of coal liquification processes). It is difficult to ascertain the carcinogenicity of the component PAHs in these mixtures because of the potential interactions that could occur and the presence of other carcinogenic substances in the mixtures. However, most of the available information on the carcinogenicity of PAHs in humans must be inferred from studies that reported the effects of exposure to complex mixtures that contain PAHs. Epidemiologic studies have shown increased mortality due to lung cancer in humans exposed to coke-oven emissions, roofing-tar emissions, and cigarette smoke. Each of these mixtures contains benzo(a)pyrene, chrysene, benz(a)anthracene, benzo(b)fluoranthene, and dibenz(a,h)anthracene as well as other potentially carcinogenic PAHs and other carcinogenic and potentially carcinogenic chemicals, tumor promoters, initiators, and cocarcinogens such as nitrosamines, coal tar pitch, and creosote. It is thus impossible to evaluate the contribution of any individual PAH to the total carcinogenicity of these mixtures in humans because of the complexity of the mixtures and the presence of other carcinogens. Despite these limitations, reports of this nature provide qualitative evidence of the potential for mixtures containing PAHs such as benzo(a)pyrene, chrysene, benz(a)anthracene, benzo(b)fluoranthene, and dibenz(a,h)anthracene to cause cancer in humans. Several skin-painting studies have been conducted in animals using various PAHs and PAH-containing mixtures. Although many of these studies would be considered inadequate by current standards, the results nevertheless indicate that several of the 15 PAHs discussed in this profile can induce skin tumors as well as act as tumor initiators and promoters. More information on the carcinogenic potential of chronically inhaled and ingested PAHs (especiallly the less-well-studied ones) would be useful. This is particularly important for those PAHs other than benzo(a)pyrene since nonalternant PAHs may have different carcinogenic mechanisms of action than alternant PAHs such as benzo(a)pyrene, and so it may not be appropriate to extrapolate information from alternant PAHs to nonalternant PAHs.

Genotoxicity. The genotoxic potential of several of the PAHs has been extensively investigated using both in vivo and in vitro assays. The available data indicate that several PAHs [including benzo(a)pyrene] are genotoxic while others (including anthracene) are not. The existing database describes the genotoxic potential of most of the PAHs, and no additional studies are needed at this time.

Reproductive Toxicity. No information on the reproductive effects of PAHs in humans is available. Limited data are available on benzo(a)pyrene only that indicate that this PAH has a potential to induce adverse reproductive effects. Given the widespread potential for exposure to PAHs, reproductive organ pathology should be examined in any 90-day studies that may be conducted. If these preliminary data indicate that any of the PAHs may present a reproductive hazard, then multigeneration reproductive toxicity studies should be conducted. The pharmacokinetic data on PAHs are insufficient to determine whether similar effects may be expected to occur across different routes of exposure.

Developmental Toxicity. Information on the developmental effects of PAHs in humans was not found. Limited data are available on just a few PAHs [mostly benzo(a)pyrene] that indicate that ingested or parenterally administered PAHs have a potential to induce adverse developmental effects. Given the widespread potential for inhalation exposure to PAHs (particularly around hazardous waste sites) developmental toxicity studies in animals with all PAHs would be useful to assess the potential risk for PAH-induced adverse developmental effects. The pharmacokinetic data on PAHs are insufficient to determine whether similar effects may be expected to occur across different routes of exposure.

Immunotoxicity. Immunotoxicity associated with exposure to PAHs has not been observed in humans. There is information available in animals on the immunotoxicity of several PAHs following dermal exposure (contact hypersensitivity) and intraperitoneal or subcutaneous administration (suppression of both humoral and cellular immunity). In general, the degree of immunosuppression correlates with the individual PAH's carcinogenic potency. Preliminary information on the potential for the individual PAHs to induce immunotoxic effects may be obtained from 90-day studies that examine effects on lymphoid tissue and blood components. If adverse effects on these parameters are observed, then a full battery of immunotoxic tests may be warranted to further characterize the potential immunotoxicity of these PAHs.

Neurotoxicity. No information is available on the short- or long-term neurotoxic effects of exposure to PAHs in humans and animals. However, acute, -intermediate- and chronic-duration studies conducted in animals do not indicate that any of the PAHs tested showed evidence of neurotoxicity, though these tests were not designed to detect subtle neurological changes. Neurobehavioral as well as neuropathological end points should be examined in any 90-day studies that may be conducted. If these preliminary data indicate that any of the PAHs are neurotoxicants, then neurotoxicity studies in animals, using sensitive functional and neuropathological tests, would be helpful to further characterize the neurotoxic potential of these PAHs.

Epidemiological and Human Dosimetry Studies. Most of the available information on the effects of PAHs in humans comes from reports of occupational exposures to PAH-containing mixtures. Limitations inherent in these studies include unquantified exposure concentrations and durations, as well as concomitant exposure to other potentially toxic substances. Despite their inadequacies, studies in humans suggest that PAH-containing mixtures are dermal irritants and carcinogens following inhalation and/or dermal exposure. Well-controlled epidemiological studies of people living in close proximity to areas where PAHs have been detected at high levels in surface water and groundwater near hazardous waste sites, and of people occupationally exposed, could add to and clarify the existing database on PAH-induced human health effects. Particular effects to be examined should include cancer (of the skin and other organs) and other adverse skin effects. However, such studies would be difficult to conduct. Furthermore, it would be very difficult to control for confounding factors such as smoking, geographical location, lifestyle, etc.

Biomarkers of Exposure and Effect. PAHs and their metabolites (e.g., 1-hydroxypyrene) can be measured in the urine of exposed individuals. The identification of PAH metabolites in the urine could serve as a method of biological monitoring of exposed workers, and possibly individuals living in the vicinity of hazardous waste sites where PAHs have been detected. However, because of the ubiquitous nature of PAHs in the environment, detection of PAH metabolites in the body tissues or fluids is not specific for exposure to any particular source. PAHs form DNA adducts that can be measured in body tissues or blood following exposure to PAHs and mixtures that contain PAHs. Again, these PAH-DNA adducts are not specific for any particular source of PAHs (i.e., the source of exposure for these PAHs may be hazardous waste sites or ingestion of a charbroiled steak). Therefore, a biomarker of exposure specific to PAHs found at hazardous waste sites would be useful to monitor exposure to these compounds.

The available genotoxicity data indicate that several of the 15 PAHs discussed in this profile are genotoxic in both nonmammalian and mammalian systems and are indirect mutagens (i.e., requiring the presence of an exogenous mammalian metabolic system). There were no tests reported for humans exposed to benzo(a)pyrene (the most widely tested PAH) in vivo, but several types of cultured human tissue cells demonstrated positive results for benzo(a)pyrene-induced genotoxicity (as evidenced by the induction of chromosomal aberrations, sister chromatid exchange) and binding of benzo(a)pyrene to DNA. Thus, although these results are exclusively from in vitro tests and the limited genotoxicity tests conducted on urine obtained from humans exposed to creosote (a complex mixture containing PAHs) have been negative, these genotoxic effects observed in human tissue cells may serve as a biomarker of effects for at least one of the PAHs, benzo(a)pyrene. No other biomarkers (specific or otherwise) have been identified following exposure to PAHs. The formation of benzo(a)pyrene-DNA adducts has been demonstrated and this may serve as a biomarker of PAH-induced carcinogenicity. However, techniques to measure adducts of other PAHs with DNA have not yet been demonstrated, but may be useful. Sensitive studies to identify and measure effects more diagnostic of PAH-specific injury other than cancer would also be useful.

Absorption, Distribution, Metabolism, and Excretion. The presence of PAHs and their metabolites in human urine and blood following inhalation and dermal exposures indicates that PAH absorption occurs in humans. However, there were no quantitative studies that monitored the extent and rate of PAH absorption in humans. Most studies regarding the pulmonary absorption of PAHs in animals are based on intratracheal instillations. More information based on controlled inhalation exposures would be useful.

The dermal study conducted by Storer et al. (1984) revealed that several PAHs in a crude coal tar mixture, except benzo(a)pyrene, were absorbed. In contrast, other studies in animals indicate that benzo(a)pyrene was dermally absorbed. Exposure to PAHs as a mixture results in interactions between the compounds that ultimately affect their dispositions. Occupational exposure to PAHs generally occurs as a mixture. Studies exploring how PAHs interact with each other to affect their disposition would be more representative of real-life exposures.

The only studies available regarding the distribution of PAHs in humans measured PAH content in a limited number of tissues (e.g., fat, tumors). These studies do not provide information on how PAHs distribute throughout the human body following all routes of exposure. However, animal studies regarding their distribution were abundant. Qualitative similarities in distribution among species suggested that distribution in humans would also be similar.

The important aspects of fetal distribution following oral exposure were addressed by Shendrikova and Aleksandrov (1974). No studies were located regarding PAHs permeating the placenta following inhalation or dermal exposures. Since these routes of exposure are more likely at hazardous waste sites, this information would have more human relevance.

PAH metabolism has been extensively reviewed in vivo and in vitro in human and animal tissue homogenates, cultures, and perfused systems. However, these studies are limited to the biotransformation of individual compounds. Since most metabolic pathways have been identified or can be predicted for the individual PAHs, it is now important to understand how these metabolic pathways are affected when the PAHs compete. The carcinogenic and toxic potential of PAHs relies on their metabolites. Alterations in rates of metabolism and metabolite profiles may affect the toxic consequences of PAHs. Available data on several of the non-alternant tumorigenic PAHs discussed in this profile indicate that they exert their adverse effects by mechanisms that differ from those that have been more recently elucidated for alternant PAHs. More studies are needed to determine the mechanism(s) by which non-alternant PAHs such as benzo(b)fluoranthene, benzo(k)fluoranthene, and indeno(1,2,3-cd)pyrene are metabolically transformed to genotoxic agents. Once this is complete, further studies on how mixtures of PAHs can influence the ultimate activation of these PAHs can be more fully explored.

No studies were located in humans monitoring the rate and extent of PAH excretion following all routes of exposures. Most studies in animals concentrate on the extent of PAH excretion and the distribution of the compound in urine, feces, and bile. Data are limited regarding the rates of excretion and toxicokinetic parameters.

Comparative Toxicokinetics. The disposition of PAHs has been extensively reviewed in animals, but its study in humans has been very limited. The absorption and distribution of PAHs in various species would be similar based on the lipophilicity of the compounds. Qualitatively, metabolism and excretion would be similar, but variability in specific activities of enzymes will alter the metabolic profiles among the species. Knowledge of these differences in enzyme activity in various species would assist in predicting which pathways and metabolites would prevail. Therefore, a need exists to examine the metabolism of those less-well-studied PAHs in several species (i.e. rodent and nonrodent) so that the carcinogenic potential of PAHs in various species could be predicted.

2.8.3 On-going Studies

No on-going studies were identified that explored the health effects or toxicokinetics of PAHs or attempted to identify specific biomarkers of exposure or effect for PAHs. However, a document on the comparative potency approach for estimating the cancer risk associated with exposure to mixtures of PAHs is currently being developed by EPA. Once it is finalized, this approach may be used to predict the carcinogenicity of the less-well-studied PAHs and PAH-containing mixtures.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

The chemical formula, structure, synonyms, and identification numbers for the 15 PAHs are listed in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Important physical and chemical properties of the 15 PAHs are listed in Table 3-2.

TABLE 3-1. Chemical Identity of PAHs (a)

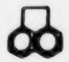
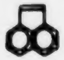
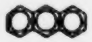
	Acenaphthene	Acenaphthylene	Anthracene
Synonyms	1,2-dihydroacenaphthylene; 1,8-dihydroacenaphthaline; 1,8-ethylenenaphthalene; 1,2-dihydroacenaphthylene	Cyclopenta[de]naphthalene	Anthracin; green oil; paranaphthalene (b) Tetra olive NZG (c) Anthracene oil
Trade names	No data	No data	No data
Chemical formula	$C_{12}H_{10}$	$C_{12}H_8$	$C_{14}H_{10}$ (b)
Chemical structure			
Wiswesser	No data	No data	L C666J
Identification numbers:			
CAS Registry	83-32-9	208-96-8	120-12-7 (b)
NIOSH RTECS	AB1000000	AB1254000	CA 9350000
EPA Hazardous Waste	No data	No data	No data
OHM/TADS	8200126	No data	8200122
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB	2659	2661	702
NCI	No data	No data	No data
STCC	No data	No data	No data

TABLE 3-1 (Continued)

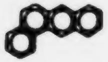
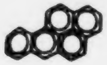
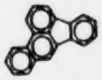
	Benzo(a)anthracene	Benzo(a)pyrene	Benzo(b)fluoranthene
Synonyms	Benz(a)anthracene 1,2-benzanthracene; benzo(b)-phenanthrene; 2,3-benzophenanthrene; tetraphene (d) BA (e)	Benzo[def]chrysene; 3,4-benzopyrene, 3,4-benzpyrene; benz[a]pyrene; BP; B[a]P (b)	3,4-Benz(e)acephenanthrylene; 2,3-benzfluoranthene; 3,4-benzfluoranthene; 2,3-benzofluoranthene; 3,4-benzofluoranthene; benzo(e)fluoranthene; B(b)f (b)
Trade names	No data	No data	No data
Chemical formula	$C_{18}H_{12}$	$C_{20}H_{12}$ (b)	$C_{20}H_{12}$ (b)
Chemical structure			
Wiswesser	L D6 B66 J	L D6 B6666 2AB TJ	L C 65 K666 1A TJ
Identification numbers:			
CAS Registry	56-55-3	50-32-8	205-99-2 (b)
NIOSH RTECS	CV 9275000 (e)	DJ3675000	CU 1400000 (c)
EPA Hazardous Waste	U018	U022	No data
OHM/TADS	800123	8200129	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB	4003	2554	4035
NCI	No data	No data	No data
STCC	No data	No data	No data

TABLE 3-1 (Continued)

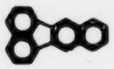
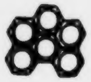
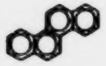
	Benzo(k)fluoranthene	Benzo(ghi)perylene	Chrysene
Synonyms	8,9-benzfluoranthene; 8,9-benzofluoranthene; 11,12-benzofluoranthene; 2,3,1,8-binaphthylene; dibenzo(bjk)fluorene (b)	1,12-benzoperylene (d)	1,2-Benzophenanthrene; benzo(a)-phenanthrene; 1,2-benzphenanthrene; benz(a)phenanthrene; 1,2,5,6-dibenzonaphthalene
Trade names	No data	No data	Not applicable (b)
Chemical formula	$C_{20}H_{12}$ (b)	$C_{22}H_{12}$ (d)	$C_{18}H_{12}$ (b)
Chemical structure			
Wiswesser	No data	No data	No data
Identification numbers:			
CAS Registry	207-08-9 (b)	191-24-2 (d)	218-01-9 (b)
NIOSH RTECS	DF 6350000 (e)	D1 6200500 (e)	GC 0700000 (e)
EPA Hazardous Waste	No data	No data	U050 (e)
OHM/TADS	No data	8200129	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB	No data	No data	2810
NCI	No data	No data	No data
STCC	No data	No data	No data

TABLE 3-1 (Continued)

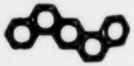
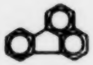
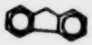
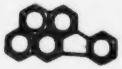
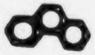
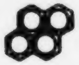
	Dibenz(a,h)anthracene	Fluoranthene	Fluorene
Synonyms	1,2,5,6-Dibenz(a,h)anthracene (d) Dibenz(a,h)anthracene, DB(a,h)A; DBA; 1,2:4,6-dibenz(a,h)anthracene; 1,2:5,6-dibenz(a)anthracene (b)	1,2-(1,8-Naphthylene)benzene; 1,2-benzacenaphthene; 1,2-(1,8-naphthalenediyl)benzene; benzo(jk)fluorene	ortho-Biphenylene methane; diphenylenemethane; 2,2-methylene biphenyl (b) 2,3-benzidene (f)
Trade names	No data	No data	No data
Chemical formula	$C_{22}H_{14}$ (b)	$C_{16}H_{10}$	$C_{13}H_{10}$ (b)
Chemical structure			
Wiswesser	L G6 B666J	L C6566 1A PJ	No data
Identification numbers:			
CAS Registry	53-70-3 (b)	206-44-0	86-73-7 (b)
NIOSH RTECS	HN 2625000 (e)	LL4025000	LL5670000
EPA Hazardous Waste	U063	U120	No data
OHM/TADS	No data	8200136	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB	5097	5486	2165
NCI	No data	No data	No data
STCC	No data	No data	No data

TABLE 3-1 (Continued)

	Indeno(1,2,3-cd)pyrene	Phenanthrene	Pyrene
Synonyms	1P; ortho-phenylenepyrene; 1,10-(ortho-phenylene)pyrene; 1,10-(1,2-phenylene)pyrene; 2,3-ortho-phenylene pyrene (b) Indenopyrene	Phenanthrene; Phenantrin (b)	Benzo(def)phenanthrene; β-pyrene (b)
Trade names	No data	No data	No data
Chemical formula	$C_{22}H_{12}$ (b)	$C_{14}H_{10}$ (b)	$C_{16}H_{10}$ (b)
Chemical structure			
Wiswesser	No data	No data	No data
Identification numbers:			
CAS Registry	193-39-5 (b)	85-01-8 (b)	129-00-00 (b)
NIOSH RTECS	NK 9300000	SF7175000	No data
EPA Hazardous Waste	U137	No data	No data
OHM/TADS	No data	8200140	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB	5101	2166	4023
NCI	No data	No data	No data
STCC	No data	No data	No data

CAS = Chemical Abstracts Services; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; and STCC = Standard Transport Commodity Code.

(a) All information obtained from HSDB 1988 except where noted.
(b) IARC 1983
(c) Callahan et al. 1979
(d) Eller 1984
(e) Sax and Lewis 1989
(f) Weast et al. 1988

TABLE 3-2. Physical and Chemical Properties of PAHs (a)

	Acenaphthene	Acenaphthylene	Anthracene
Molecular weight	154.21	154.20	178.2 (f)
Color	Orthorhombic bipyramidal needles from alcohol, white Needles	Prisms from ether; plates from alcohol	Tablet or monoclinic prism when pure (f) Colorless with violet fluorescence when pure; yellow with green fluorescence when impure
Physical state	Solid (needles)	Solid (prism/plate)	Solid (tablet or prism) (f)
Melting point	95°C	92-93°C	218°C (f)
Boiling point	96.2°C	265-275°C	342°C (f) 340°C (b)
Density	1.225 at 0°C 1.0242 at 0°/4°C (b)	0.8988 at 16°C/2°C	1.25 at 27°/4°C 1.283 at 25°/4°C (b)
Odor	No data	No data	Weak aromatic odor
Odor threshold:	Threshold odor concentration [TOC] in water at room temperature	No data	No data
Water	0.08 ppm, range 0.02-0.22 ppm	No data	No data
Air	8.0×10^{-2} ppm	No data	No data
Solubility:			
Water	Insoluble	3.93 mg/L water	Virtually insoluble in water (f)
Organic solvents	Soluble in alcohol, methanol, propanol, chloroform, benzene, toluene, glacial acetic acid	Alcohol, ether, benzene	Benzene, carbon disulphide, carbon tetrachloride, chloroform, ether, ethanol, methanol, toluene (f) Acetone (b)
Partition coefficients	$K_{ow} = 9.6\times10^3$, $K_{oc} = 4.6\times10^3$ (c)	$\log K_{ow} = 4.07$ $K_{ow} = 5.3\times10^3$; $K_{oc} = 2.5\times10^3$ (c)	$\log K_{ow} = 4.45$ $K_{oc} = 1.4\times10^4$; $K_{ow} = 2.8\times10^4$ (c)
Vapor pressure:	4.47×10^{-3} mmHg (d)	0.029 torr (20°C) (c)	1 mm at 145°C (f) 1.7×10^{-5} torr at 25°C (c)
Henry's law constant	No data	1.45×10^{-3}	8.6×10^{-5} (c)
Autoignition temperature	No data	No data	540°C 1004°F (g)
Flashpoint	No data	No data	250°F
Flammability limits	Dust is moderately flammable (e)	No data	No data
Conversion factors	No data	No data	No data

TABLE 3-2 (Continued)

	Benzo(a)anthracene	Benzo(a)pyrene	Benzo(b)fluoranthene
Molecular weight	228.29 (h)	252.3 (f)	252.3 (f)
Color	Plates with yellow-blue fluorescence (recrystallized from glacial acetic acid or ethane) (b)	Pale yellow; fluoresces (f) yellow-green in ultraviolet light (i)	Colorless needles (f) Needles recrystallized from benzene (b)
Physical state	Solid (plates)	Plates or needles (i) (recrystallized from benzene/ligroin)	Solid (needles) (b)
Melting point	158-159°C (h) 162°C (b)	179-179.3°C (i)	168.3°C (f)
Boiling point	400°C (g) 435°C sublimes (i)	310-312°C (at mm Hg) (i) 495°C (at mm Hg) (j)	No data
Density	1.274 (20°C)	1.351	No data
Odor	No data	Unknown	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	Virtually insoluble (9-14 μg/L) (f)	$3.8x10^{-6}$ g/L (c)	14 μg/L (c) Virtually insoluble in water (f)
Organic solvents	Slightly soluble in acetic acid and hot ethanol; soluble in acetone and diethyl ether; very soluble in benzene (f)	Sparingly soluble in ethanol and methanol; soluble in benzene, toluene, xylene, and ether (f)	Slightly soluble in benzene, acetone (f)
Partition coefficients	$K_{ow} = 4.1x10^5$, $K_{oc} = 2x10^5$ (c)	$k_{ow} = 1.55x10^6$ (c) $\log k_{ow} = 6.06$ $k_{oc} = 5.5x10^6$ (c)	$K_{ow} = 1.1x10^6$; $K_{oc} = 5.5x10^5$ (c)
Vapor pressure:	$2.2x10^{-8}$ torr (20°C)	$5.6x10^{-9}$mm Hg (c)	$10^{-11} \rightarrow 10^{-6}$ torr at 20°C (c)
Henry's law constant	$1x10^{-6}$	$4.9x10^{-7}$ atm-m^3/mol (c)	$1.22x10^{-5}$ (c)
Autoignition temperature	No data	Unknown	No data
Flashpoint	No data	Unknown	No data
Flammability limits	No data	Unknown	No data
Conversion factors	No data	1 ppm = 10.32 mg/m^3 (l)	No data

TABLE 3-2 (Continued)

	Benzo(k)fluoranthene	Benzo(ghi)perylene	Chrysene
Molecular weight	252.3 (f)	276.34 (h)	228.3 (f)
Color	Pale yellow needles (f)	No data	Colorless with blue fluorescence; othorhombic bipyramidal plates (recrystallized from benzene) (f) Red with blue fluorescence (recrystallized from benzene or acetic acid) (b)
Physical state	Solid (needles)	No data	Solid (plates) (b)
Melting point	215.7°C (f)	273°C (h)	255-256°C (f)
Boiling point	480°C (f)	222°C (c)	448°C (f)
Density	No data	No data	1.274 (g)
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	Virtually insoluble (f)	2.6x10^{-4} g/L 25°C (c)	Virtually insoluble in water (1.5-2.2 μg/L) (f)
Organic solvents	Soluble in benzene, acetic acid, ethanol (f)	No data	Slightly soluble in acetone, carbon disulphide, diethyl ether, ethanol (1 g/1300 ml ethanol), glacial acetic acid toluene 10.24 parts/100 parts at 18°C 1 g/480 ml at 20°C; 5% at 100°C), hot xylene. Soluble in benzene. (f) Moderately soluble in boiling benzene (g)
Partition coefficients	K_{ow} = 1.15x10^6; K_{ow} = 5.5x10^5 (c)	K_{ow} = 3.2x10^6; K_{oc} = 1.6x10^6 (c)	K_{ow} = 4.1x10^5; K_{oc} = 2x10^5 (c)
Vapor pressure:	5x10^{-7} (20°C) torr (c)	1.03x10^{-10} (25°C) torr (c)	6.3x10^{-9} mmHg (25°C) (c)
Henry's law constant	3.87x10^{-5} (c)	1.44x10^{-7} (c)	1.05x10^{-6} (c)
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	No data	No data	No data

TABLE 3-2 (Continued)

	Dibenz(a,h)anthracene	Fluoranthene	Fluorene
Molecular weight	278.35 (h)	202.26	166.2 (f)
Color	Colorless (f) Plates (recrystallized from acetone) leaflets (recrystallized from acetic acid) (b)	Colored needles; pale yellow needles or plates from alcohol	White when recrystallized from ethanol (f)
Physical state	Solid (plates or leaflets) (b)	Solid (needles or plates)	Solid (leaflets or flakes; crystalline plates) (f)
Melting point	262°C (h)	111°C	116-117°C (f)
Boiling point	269-270°C	375°C	295°C (f)
Density	1.282	1.252 at 0°C/4°C	1.203 at 0°C/4°C
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	0.5 µg/L (f)	Almost insoluble in water (0.20-0.26 mg/L) (f)	Almost insoluble in water (1.68-1.98 mg/L) (f)
Organic solvents	Slightly soluble in ethyl alcohol; soluble in acetone, acetic acid, benzene, toluene and xylene (b)	Alcohol, ether, benzene, acetic acid	Acetic acid, acetone, benzene, carbon disulphide, carbon tetrachloride, diethyl ether, ethanol, pyrimidine, solution, toluene (f)
Partition coefficients	K_{ow} 6.9 x10^6; K_{oc} = 3.3x10^6 (c)	log K_{ow} 4.90; K_{oc} = 3.8x10^4 K_{ow} = 7.9x10^4; K_{oc} = 3.8x10^4 (c)	K_{ow} = 1.5x10^4; K_{oc} = 7.3x10^3 (c)
Vapor pressure:	1x10^{-10} mmHg at 20°C (c)	0.01 mmHg (20°C) 5.0x10^{-6} torr (25°C) (c)	10 mm at 146°C (f) 7.1x10^{-4} torr (c)
Henry's law constant	7.3x10^{-8} (c)	6.5x10^{-6} (c)	6.4x10^{-5} (c)
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	No data	No data	No data

TABLE 3-2 (Continued)

	Indeno(1,2,3-cd)pyrene	Phenanthrene	Pyrene
Molecular weight	276.3 (f)	178.2 (f)	202.3 (f)
Color	Yellow plates or needles showing a greenish-yellow fluorescence (f)	Monoclinic plates (recrystallized from ethanol) colorless, shining crystals; leaflets (f)	Pale yellow plates (recrystallized from toluene) monoclinic prismatic tablets with a slight blue fluorescens (recrystallized from ethanol or sublimation) (f)
Physical state	Solid (plates or needles) (f)		Colorless solid
Melting point	163.6°C (f)	100°C (f)	156°C 153-155°C 156°C (k)
Boiling point	530°C	340°C (f)	393°C (b) 404°C (k)
Density	No data	0.900 at 4°C	1.271 at 23°C Boiling point 393°C
Odor	No data	Faint aromatic odor	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	Insoluble in water (f)	Virtually insoluble in water (1-1.6 mg/L) (f)	Virtually insolbule in water (129-165 µg/L) (f)
Organic solvents	Soluble in organic solvents (f)	Soluble glacial acetic acid; 1 g dissolves in the following volumes: 2 ml benzene, 1 ml carbon disulphide, 2.4 ml carbon tetrachloride, 3.3 ml anhydrous diethyl ether, 60 ml cold ethanol, 25 nl absolute ethanl, 10 ml boiling 95% ethanol, and 2.4 ml toluene (f)	Soluble in benzene, carbon disulphide, diethyl ether, ethanol, petroleum ether, toluene, race tone (f) Alcohol
Partition coefficients	log K_{ow} 6.584 K_{ow} = $3.2x10^6$; K_{oc} = $1.6x10^6$ (c)	4.57 K_{ow} = $2.8x10^4$; K_{oc} = 1.4 $x10^4$ (c)	Octanol/water: log K_{ow} = 4.88 K_{ow} = $8.0x10^4$; K_{oc} = $3.8x10^4$ (c)
Vapor pressure:	~10^{-10} torr (20°C) (c)	$9.6x10^{-4}$ torr (25°C) (c)	$2.5x10^{-6}$ torr at 25°C (c)
Henry's law constant	$6.95x10^{-8}$ (c)	$2.26x10^{-4}$ (c)	$5.1x10^{-6}$ (c)
Autoignition temperature	No data	No data	No data

TABLE 3-2 (Continued)

	Indeno(1,2,3-cd)pyrene	Phenanthrene	Pyrene
Flashpoint	No data	171°C	No data
Flammability limits	No data	No data	No data
Conversion factors	No data	No data	No data

(a) All information obtained from HSDB 1988 except where noted.
(b) Weast et al. 1988
(c) Mabey et al. 1982
(d) EPA 1987a
(e) ITII 1982
(f) IARC 1983
(g) Sax and Lewis 1989
(h) Eller 1984
(i) Weast 1987
(j) Aldrich 1986
(k) Windholz 1983
(l) Verschueren 1983

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

The primary source of many PAHs in air is the incomplete combustion of wood and fuel (Perwak et al. 1982). As such, PAHs are a ubiquitous product of combustion from common sources such as motor vehicles and other gas burning engines, wood burning stoves and furnaces, cigarette smoke, industrial smoke or soot, and charcoal-broiled foods (IARC 1983). Natural sources include volcanoes, forest fires, crude oil, and shale oil (HSDB 1988).

The composition, either in concentration or percent weight, in which several PAHs appear in various substances is given below. A coal tar sample has been found to contain approximately 0.007 mg/kg benz(a)anthracene, 3,000 mg/kg benzo(b)fluoranthene, 4 g/kg chrysene, and 30 mg/kg benzo(a)pyrene (Perwak et al. 1982). High-temperature coal tar contains 1,000 mg/kg dibenz(a,h)anthracene (IARC 1985). A sample of coal tar pitch was found to contain less than 10 mg/kg benz(a)anthracene, less than 10 mg/kg chrysene, and approximately 10 mg/kg benzo(a)pyrene; creosote oil contains less than 3 mg/kg benz(a)anthracene, less than 1 mg/kg chrysene, and less than 10 mg/kg benzo(a)pyrene (Perwak et al. 1982). Creosote contains 21% phenanthrene, 10% fluorene and 10% fluoranthene. Smaller amounts of other PAHs as well as other substances make up the remainder of creosote (Lorenz and Gjovik 1972).

Catalytic degradation of acenaphthene results in acenaphthylene (Grayson 1978). Acenaphthene is manufactured by passing ethylene and benzene or napthalene through a red hot tube or by heating tetrahydroacenaphthene with sulfur to 180°C. It can also be made from acenaphthenone or acenaphthenequinone by high-pressure hydrogenation in decalin with nickel at 180°-240°C (Windholz 1983). Another manufacturing process involves the isolation and recovery from a concentrated tar-distillation fraction (Grayson 1978).

Anthracene is produced commercially by recovery from the coal tar distillation fraction known as "anthracene oil" or "green oil." Purification techniques including heating and vacuum distillation are required to remove the major contaminant, potassium carbazole (IARC 1985). Zone melting of solid anthracene and crystallization from benzene followed by sublimation are also effective purification techniques (Hampel and Hawley 1973).

The following compounds are not commercially produced in the United States: benz(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(ghi)perylene, benzo(a)pyrene, dibenz(a,h)anthracene, fluoranthene, fluorene, indeno(1,2,3-cd)pyrene, phenanthrene, or pyrene (IARC 1985).

Although the primary source of chrysene in air is from the incomplete combustion of heating materials as described above, chrysene also occurs in coal tar formed during the distillation of coal. In addition, chrysene is formed in very small amounts during the distillation or pyrolysis of many fats or oils. Chrysene can be synthesized by heating hydrogen and acetylene to 800°C.

4.2 IMPORT/EXPORT

In 1982, 1.15×10^5 kg of anthracene were imported to the United States (HSDB 1988). In 1984, 6.49×10^4 kg of acenaphthene, 91 kg of fluorene, 551 kg of phenanthrene, and 9,440 kg of fluoranthene were imported into the United States (USDOC 1985). In 1985, the United States imported a total of almost 12 million gallons of creosote oil from the Netherlands, France, West Germany, and other countries and almost 185 million pounds of coal tar pitch, blast furnace tar, and oil-gas tar from Canada, Mexico, West Germany, Australia, and other countries (USDOC 1985).

4.3 USE

There is no known use for benz(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(ghi)perylene, benzo(a)pyrene, dibenz(a,h)-anthracene, indeno(1,2,3-cd)pyrene, or pyrene except as a research chemical (Hawley 1987).

Anthracene is used as an intermediate in dye production. It is also used in smoke screens, scintillation counter crystals, and organic semiconductor research (Hawley 1987). Anthracene is used to synthesize the chemotherapeutic agent, Amsacrine (Wadler et al. 1986). Acenaphthene is used as a dye intermediate in the manufacture of plastics, as an insecticide and fungicide Windholz 1983).

Fluorene is used as a chemical intermediate in many chemical processes and in the formation of polyradicals (HSDB 1988). Phenanthrene is used in the manufacture of dyestuffs and explosives and in biological research (Hawley 1987). Fluoranthene is used as a lining material to protect the interior of steel and ductile-iron drinking water pipes and storage tanks (NRC 1983).

4.4 DISPOSAL

The criteria for land treatment or burial in a sanitary landfill and disposal practices are undergoing significant revision (HSDB 1988). Approximately one-third of a PAH solution is particle-bound and can be removed by sedimentation, flocculation, and filtration processes. The remaining dissolved PAH usually requires oxidation for partial removal/transformation (EPA 1980).

Acenaphthene, indeno(1,2,3-cd)pyrene, and fluoranthene are all good candidates for rotary kiln incineration at temperatures ranging from 820°C to 1,600°C (EPA 1981). Benz(a)anthracene and benzo(a)pyrene wastes can be oxidized using agents such as concentrated sulfuric acid, potassium dichromate, or potassium permanganate (IARC 1985). Water contaminated with anthracene can be destroyed by sorption with powdered activated charcoal, filtration through a granular-activated carbon bed, and chemical oxidation with potassium permanganate (HSDB 1988).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

This chapter provides a discussion of the environmental fate and potential for human exposure to 15 PAHs. For the purposes of describing environmental fate, these PAHs have been grouped into low, medium, and high molecular weight classes (see Section 5.3.1, Transport and Partitioning). In general, chemicals within each class have similar environmental fates. When available, data are provided for the individual PAHs that are the subject of the profile. When data on each compound are not available, data on members of the weight class are provided. Data regarding total PAHs or generalizations about PAHs are also used to provide insight into the behavior of the compounds covered in this report.

PAHs are released to the environment through natural and man-made sources with emissions largely to the atmosphere. Natural sources include emissions from volcanoes and forest fires. Man-made sources provide a much greater release volume than natural sources; the largest single source is the burning of wood in homes. Automobile and truck emissions are also major sources of PAHs. Hazardous waste sites can be a concentrated source of PAHs on a local scale. Examples of such sites are abandoned wood-treatment plants (sources of creosote) and former manufactured-gas sites (sources of coal tar). PAHs can enter surface water through atmospheric deposition and from discharges of industrial effluents (including wood-treatment plants), municipal wastewater, and improper disposal of used motor oil. Several of the PAHs have been detected at hazardous waste sites at elevated levels. In air, PAHs are found sorbed to particulates and as gases. Particle-bound PAHs can be transported long distances and are removed from the atmosphere through precipitation and dry deposition. PAHs are transported from surface waters by volatilization and sorption to settling particles. The compounds are transformed in surface waters by photooxidation, chemical oxidation, and microbial metabolism. In soil and sediments, microbial metabolism is the major process for degradation of PAHs. Although PAHs are accumulated in terrestrial and aquatic plants, fish, and invertebrates, many animals are able to metabolize and eliminate these compounds. Bioconcentration factors (BCFs) for fish and crustaceans are frequently in the 100-2000 range. Food chain uptake does not appear to be a major source of exposure to PAHs for aquatic animals.

The greatest sources of exposure to PAHs for most of the U.S. population are active or passive inhalation of the compounds in tobacco smoke, wood smoke, and contaminated air, and ingestion of the compounds in foodstuffs. The general population may also be exposed to PAHs in drinking water and food, and through skin contact with soot and tars. Higher than background levels of PAHs are found in foods that are grilled or smoked. The average total daily intake of PAHs by a member of the general population has been estimated to be 0.207 μg from air, 0.027 μg from water, and 0.16-1.6 μg from food. Workers may be exposed to PAHs through inhalation of engine exhaust and the use of PAH-containing products (e.g., in mining, chemical, transportation, and electrical industries). Populations with potentially high exposure to PAHs include workers in these industries and members of the general population who smoke or consume food or water contaminated with these compounds. Persons living in the vicinity of hazardous waste sites where PAHs have been detected above background levels may also be exposed to higher levels.

5.2 RELEASES TO THE ENVIRONMENT

PAHs are widely distributed in the environment, and have been detected in air, water, sediment, soil, food, and other consumer products. The number of NPL sites at which the individual PAHs have been found is given in Table 5-1. The frequency of these sites within the United States can be seen in Figure 5-1. EPA's Contract Laboratory Program (CLP 1988) statistical database indicates that PAHs have been detected at over 71% of the 2,783 hazardous waste sites that have had samples of all media analyzed by the CLP. The percentage of sites at which the individual PAHs have been detected are summarized in Table 5-2.

5.2.1 Air

Most of the direct releases of PAHs to the environment are to the atmosphere. The residential burning of wood is the largest source of these PAHs; releases are primarily the result of inefficient combustion and uncontrolled emissions (NRC 1983). Other important sources include automobile exhaust, industrial power generation, incinerators, and the production of coal tar, coke, asphalt, and petroleum catalytic cracking (Guerin 1978; Perwak et al. 1982; Santodonato 1981). The primary natural sources of airborne PAHs are forest fires and volcanoes. NRC (1983) estimated the U.S. annual emission in metric tons (from early to mid-1970s) of polycyclic organic matter [a term generally used to describe PAHs, their nitrogen-containing analogues, and their quinone degradation products (Santodonato et al. 1981)] as follows: open burning--4,024, residential heating--3,956, automobiles and trucks--2,266, and industrial boilers--74. NRC (1983) estimated that the total amount of benzo(a)pyrene produced in the United States is between 300 and 1,300 metric tons annually.

The composition of PAH emissions varies with the combustion source. For example, emissions from residential wood combustion contain more acenaphthylene than other PAHs (Perwak et al. 1982), whereas auto emissions contain more benzo(ghi)perylene and pyrene (Santodonato 1981). In coal tar pitch emissions, concentrations of phenanthrene and pyrene are 20-80 times greater than the concentrations of benzo(a)pyrene and benzo(ghi)perylene (Sawicki 1962).

TABLE 5-1. PAH Compounds Found at National Priorities List (NPL) Sites[a]

Compound	Number of NPL Sites at which Compound has been found
Acenaphthene	25
Acenaphthylene	11
Anthracene	42
Benz(a)anthracene	35
Benzo(a)pyrene	84
Benzo(b)fluoranthene	26
Benzo(ghi)perylene	8
Benzo(k)fluoranthene	13
Chrysene	40
Dibenz(a,h)anthracene	6
Fluoranthene	56
Fluorene	33
Indeno(1,2,3-cd)pyrene	9
Phenanthrene	64
Pyrene	48

[a] There are a total of 1177 sites on the NPL (VIEW 1989).

Source: VIEW Database 1989.

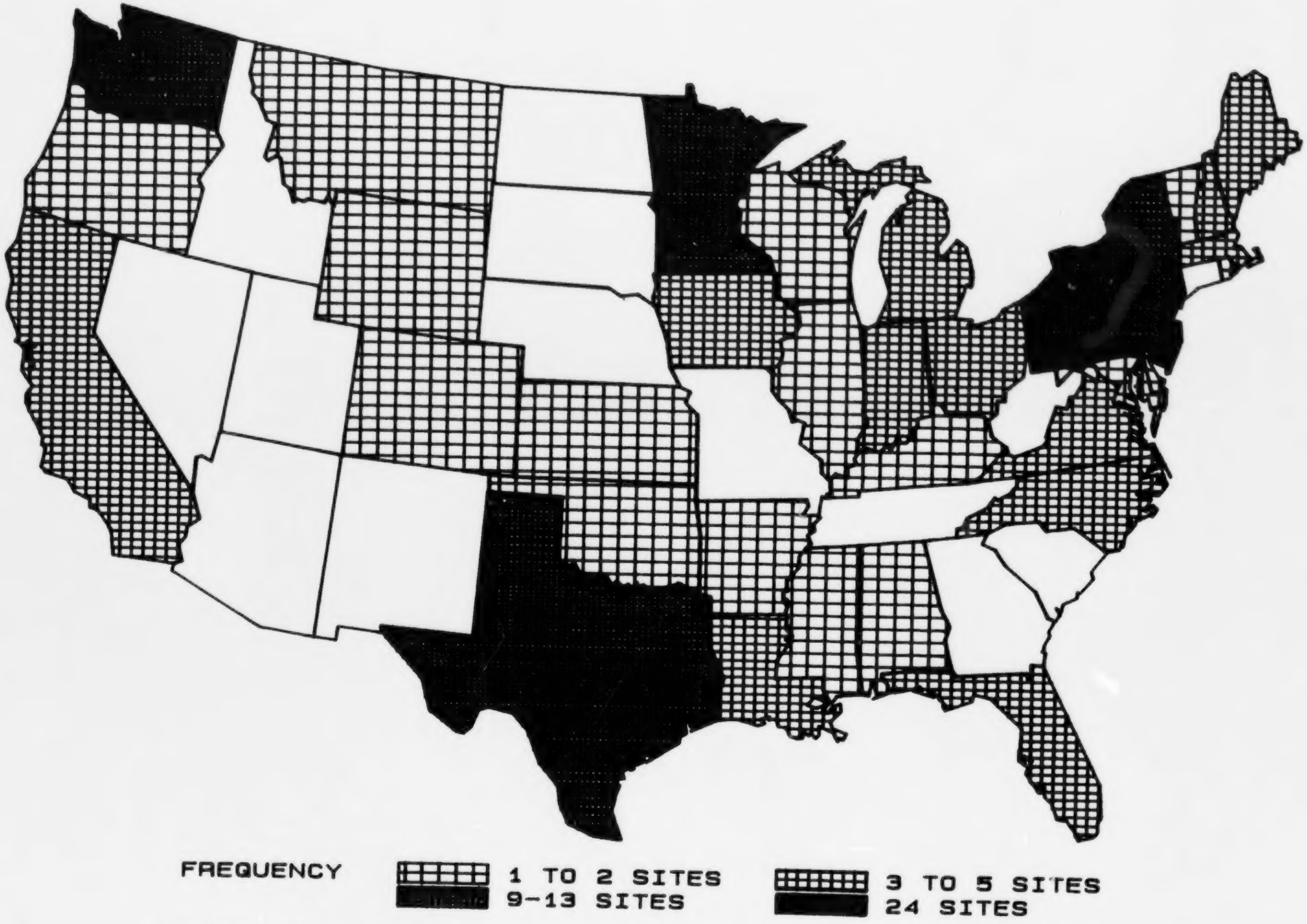

FREQUENCY
1 TO 2 SITES
3 TO 5 SITES
9-13 SITES
24 SITES

FIGURE 5-1. FREQUENCY OF SITES WITH PAHs CONTAMINATION

TABLE 5-2. Detection of the Individual PAH Compounds at the Hazardous Waste Sites That Have Had Samples Analyzed by EPA's Contract Laboratory Program (CLP) -- Summary for All Media

Compound	Site Percent (%)[a]
Acenaphthene	25
Acenaphthylene	20
Anthracene	30
Benz(a)anthracene	47
Benzo(a)pyrene	41
Benzo(b)fluoranthene	48
Benzo(ghi)perylene	1
Benzo(k)fluoranthene	30
Chrysene	50
Dibenz(a,h)anthracene	15
Fluoranthene	69
Fluorene	19
Indeno(1,2,3-cd)pyrene	26
Phenanthrene	60
Pyrene	71

[a] There are a total of 2,783 hazardous waste sites that have had samples of all media analyzed by the CLP (CLP 1988).

Source: CLP 1988

5.2.2 Water

Important sources of PAHs in surface waters include deposition of airborne PAHs (Jensen 1984), municipal wastewater discharge (Barrick 1982), urban storm water runoff (MacKenzie and Hunter 1979), runoff from coal storage areas (Stahl et al. 1984; Wachter and Blackwood 1979), effluents from wood-treatment plants and other industries (Snider and Manning 1982; USDA 1980), oil spills (Giger and Blumer 1974), and petroleum pressing (Guerin 1978). Brown and Weiss (1978) estimated that, in 1977, 1-2 tons of benzo(a)pyrene were released from municipal sewage effluents and 0.1-0.4 tons of benzo(a)pyrene were released from petroleum refinery wastewaters in the United States.

Most of the PAHs in surface waters are believed to result from atmospheric deposition (Santodonato 1981). Jensen (1984) studied benzo(a)pyrene loading to a marine coastal area and determined that atmospheric deposition was indeed the major source of benzo(a)pyrene, with lesser amounts contributed by refinery effluent, municipal waste water, urban runoff, and rivers. However, for any given body of water, the major source of PAHs could vary. Prahl et al. (1984) found that PAHs adsorbed to suspended sediments in rivers were the major source of PAHs in a Washington coastal area, and other studies have identified industrial effluents, road runoff, and oil spills as the major contributors in specific bodies of water (Santodonato 1981).

PAHs have been detected in groundwater from more than 128 of the 2,783 hazardous waste sites that have had samples analyzed by the CLP (1988). The geometric mean concentrations of PAHs from those sites at which they were detected ranged from 0.5 μg/L (benzo[b]fluoranthene and benzo[k]fluoranthene) to 2,500 μg/L (fluorene) (see Table 5-3 for the frequencies and geometric mean concentration values for the individual PAHs). PAHs have also been detected in surface water samples from more than 114 of the 2,783 sites in the CLP statistical database; the geometric mean concentrations ranged from 6.3 μg/L [dibenz(a,h)anthracene] to 77.2 μg/L (fluorene) (see Table 5-3).

5.2.3 Soil

Most of the PAHs in soil are believed to result from atmospheric deposition after local and long-range transport. The presence of PAHs in the soil of regions remote from any industrial activity supports this contention (Thomas 1986). Other potential sources of PAHs in soil include sludge disposal from public sewage treatment plants, automotive exhaust, irrigation with coke oven effluent, leachate from bituminous coal storage sites, and use of soil compost and fertilizers (Perwak et al. 1982; Santodonato 1981; Stahl et al. 1984; White and Lee 1980).

PAHs have been detected with geometric mean concentrations ranging from 828 ppb (dibenz(a,h)anthracene) to 8,024 ppb (fluorene) in soil samples

TABLE 5-3. Detection of the Individual PAH Compounds in Groundwater and Surface Water at the Hazardous Waste Sites That Have Had Samples Analyzed by EPA's Contract Laboratory Program (CLP)

	Ground Water		Surface Water	
Compound	Percentage of Sites at which Compound was Detected (%)[a]	Geometric Mean Concentration (μg/L)[b]	Percentage of Sites at which Compound was Detected (%)[a]	Geometric Mean Concentration (μg/L)
Acenaphthene	3.6	17.4	3.4	17.9
Acenaphthylene	2.2	58.4	1.6	43.4
Anthracene	1.3	8.60	1.4	12.6
Benz(a)anthracene	1.0	NR	1.3	16.4
Benzo(a)pyrene	2.6	19.0	1.6	19.0
Benzo(b)fluoranthene	1.8	0.5	2.1	33.5
Benzo(ghi)perylene	0.8	NR	1.4	10.7
Benzo(k)fluoranthene	0.8	0.5	1.0	20.0
Chrysene	1.3	NR	2.0	25.7
Dibenz(a,h)anthracene	0.9	NR	1.0	6.3
Fluoranthene	4.3	37.6	3.4	44.0
Fluorene	1.3	2,500	1.6	77.2
Indeno(1,2,3-cd)pyrene	0.6	NR	0.9	9.9
Phenanthrene	4.6	40.6	3.9	64.7
Pyrene	4.1	13.8	4.1	7.2

[a] There are a total of 2,783 hazardous waste sites that have had samples analyzed by the CLP (CLP 1988).

[b] Calculated using data from all sites at which the PAH was detected.

NR = Not reported.

Source: CLP 1988

collected from more than 1,756 of the 2,783 hazardous waste sites that have had samples analyzed by the CLP (1988) (see Table 5-4 for the frequencies and geometric mean concentration values for individual PAHs).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The global movements of PAHs can be summarized as follows: PAHs released to the atmosphere are subject to short- and long-range transport and are removed by wet and dry deposition. In surface water, PAHs can volatilize, photodegrade, oxidize, biodegrade, bind to particulates, or accumulate in aquatic organisms (with bioconcentration factors often in the 100-2,000 range). In sediments, PAHs can biodegrade or accumulate in aquatic organisms. PAHs in soil can biodegrade or accumulate in plants; PAHs can enter groundwater and be transported within an aquifer.

Transport and partitioning of PAHs in the environment are determined to a large extent by physical/chemical properties such as water solubility, vapor pressure, Henry's law constant, octanol-water partition coefficient (K_{ow}), and organic carbon partition coefficient (K_{oc}). In general, PAHs have low water solubilities. The Henry's law constant is the partition coefficient that expresses the ratio of the chemical's concentrations in air and water at equilibrium, and is used as an indicator of a chemical's potential to volatilize. The K_{oc} indicates the chemical's potential to bind to organic carbon in soil and sediment. The K_{ow} is used to estimate the potential for an organic chemical to move from water into lipid, and has been correlated with bioconcentration in aquatic organisms. Some of the transport and partitioning characteristics (e.g., Henry's law constant, K_{oc} values, and K_{ow} values) of the 15 PAHs are roughly correlated to their molecular weights. These properties are discussed by grouping these PAHs as follows:

- Low molecular weight compounds (152-178 g/mol) -- acenaphthene, acenaphthylene, anthracene, fluorene, and phenanthrene;
- Medium molecular weight compounds (202 grams/mol) -- fluoranthene and pyrene;
- high molecular weight compounds (228-278 grams/mol) -- benz(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(ghi)perylene, benzo(a)pyrene, chrysene, dibenz(a,h)anthracene, and indeno(1,2,3-cd)pyrene.

PAHs are present in the atmosphere in the gaseous phase or sorbed to particulates. The ratio of particulate to gaseous PAHs in air samples collected in Antwerp, Belgium, was 0.03 for anthracene, 0.49 for pyrene, 3.15 for summed benz(a)anthracene and chrysene, and 11.5 for summed benzo(a)fluoranthene and benzo(b)fluoranthene (NRC 1983). Atmospheric

TABLE 5-4. Detection of the Individual PAH Compounds in Soil at the Hazardous Waste Sites That Have Had Samples Analyzed by EPA's Contract Laboratory Program (CLP)

Compound	Percentage of Sites at which Compound was Detected (%)[a]	Geometric Mean Concentration (ppb)
Acenaphthene	18.1	4,699
Acenaphthylene	16.1	1,287
Anthracene	27.7	1,707
Benz(a)anthracene	44.5	2,320
Benzo(a)pyrene	36.6	3,101
Benzo(b)fluoranthene	44.4	2,609
Benzo(ghi)perylene	24.6	1,922
Benzo(k)fluoranthene	27.8	2,486
Chrysene	46.9	2,564
Dibenz(a,h)anthracene	13.2	828
Fluoranthene	61.7	1,964
Fluorene	16.5	8,024
Indeno(1,2,3-cd)pyrene	24.5	2,514
Phenanthrene	51.5	1,879
Pyrene	63.1	1,808

[a] There are a total of 2,783 hazardous waste sites that have had samples analyzed by the CLP (CLP 1988).

Source: CLP 1988

residence time and transport distance depend on the size of the particles to which PAHs are sorbed. Larger particles emitted from urban sources tend to settle onto streets and become part of urban runoff. PAHs in urban air are primarily associated with submicron diameter soot particles that have residence times of weeks and are subject to long-range transport (Butler and Crossley 1981). Long-range transport of PAHs was examined by Lunde and Bjørseth (1977), Bjørseth et al. (1978a) and Bjørseth and Olufsen (1983) who found that PAHs originating in Great Britain could be collected in Norway and Sweden. PAHs are removed from the atmosphere by both wet and dry deposition; the relative importance of each process varies with the individual PAH. For example, Perwak et al. (1982) estimated that a total of 23% of benzo(a)pyrene released to the atmosphere is deposited on soil and water surfaces. Dry deposition of benzo(a)pyrene adsorbed onto atmospheric aerosols accounts for most of the removal; wet deposition is less significant by a factor of 3 to 5.

PAH compounds tend to be removed from the water column by volatilization to the atmosphere, binding to particulates or sediments, or by being accumulated by or sorbed onto aquatic biota. The low molecular weight PAHs have Henry's law constants in the range of 10^{-3} to 10^{-5} atm-m^3/mol; medium molecular weight PAHs have constants in the 10^{-6} range; and high molecular weight PAHs have values in the range of 10^{-5} to 10^{-8}. Compounds with values ranging from 10^{-3} to 10^{-5} are associated with significant volatilization, while compounds with values less than 10^{-5} volatilize from water only to a limited extent (Lyman et al. 1982). Half-lives for volatilization of benz(a)anthracene and benzo(a)pyrene (high molecular weight PAHs) from water have been estimated to be greater than 100 hours (Southworth 1979). Southworth et al. (1978) stated that lower molecular weight PAHs could be substantially removed by volatilization if suitable conditions (high temperature, low depth, high wind) were present. Southworth (1979) estimated half-lives for volatilization of anthracene (a low molecular weight PAH) of 18 hours in a stream with moderate current and wind, versus about 300 hours in a 1-meter-deep body of water with no current.

Because of their low solubility, PAHs in aquatic systems are primarily found sorbed to particles that either have settled to the bottom or are suspended in the water column. In an estuary, volatilization and adsorption to suspended sediments with subsequent deposition are the primary removal processes for medium and high molecular weight PAHs, whereas volatilization and microbial degradation (see Section 5.3.2.2) are the major removal processes for low molecular weight compounds (Readman et al. 1982). In an enclosed marine ecosystem study, less than 1% of the original amount of radiolabeled benz(a)anthracene added to the system remained in the water column after 30 days; losses were attributed to adsorption to settling particles and to a lesser extent to photodegradation (Hinga and Pilson 1987).

The K_{oc} indicates the chemical's potential to bind to organic carbon in soil and sediment. The low molecular weight PAHs have K_{oc} values in the range of 10^3 to 10^4, which indicates a moderate potential to be adsorbed to organic carbon in the soil and sediments. The medium molecular weight compounds have K_{oc} values in the 10^4 range. High molecular weight PAHs have K_{oc} values in the range of 10^5 to 10^6 which indicates stronger tendencies to adsorb to organic carbon. PAHs from lands cleared by slash and burn methods have been found to be deposited in charred litter and move into soils by partitioning and leaching (Sullivan and Mix 1985). Phenanthrene and fluoranthene (low and medium molecular weight PAHs, respectively) from these areas were incorporated into soil to a greater extent than high molecular weight PAHs such as benzo(ghi)pyrene and indeno(1,2,3-cd)pyrene.

Sorption of PAHs to soil and sediments increases with increasing organic carbon content and is also directly dependent on particle size. Karickhoff et al. (1979) reported partition coefficients (Kp) for sorption of pyrene to sediments as follows: sand 9.4 to 68; silt 1,500 to 3,600; and clay 1,400 to 3,800. Gardner et al. (1979) found that three to four times more anthracene and about twice as much fluoranthene, benz(a)anthracene, and benzo(a)pyrene were retained by marsh sediment than by sand. PAHs may also volatilize from soil. Volatilization of acenaphthene, anthracene, fluorene, and phenanthrene (low molecular weight PAHs) from soil may be substantial (Coover and Sims 1987). Lower molecular weight compounds may also volatilize from sediments whereas this process is not significant for the higher molecular weight compounds (Southworth 1979).

PAHs have been detected in groundwater either as a result of migration directly from contaminated surface waters or through the soil (Ehrlich et al. 1982; Wilson et al. 1986). Fluorene from an abandoned creosoting pit migrated through sand and clay into groundwater (Wilson et al. 1986). PAHs have also been shown to be transported laterally within contaminated aquifers (Ehrlich et al. 1982).

PAHs can be accumulated in aquatic organisms from water, sediments, and food. Bioconcentration factors (BCFs) of PAHs in fish and crustaceans have frequently been reported to be in the range of 100 to 2000 (Eisler 1987). In general, bioconcentration was greater for the higher molecular weight compounds than for the lower molecular weight compounds. Bioconcentration experiments performed with radiolabeled compounds may overstate the bioconcentration of parent compounds. Spacie et al. (1983) estimated BCFs of 900 for anthracene and 4,900 for benzo(a)pyrene in bluegills (whole body) based on total radiolabeled carbon (^{14}C) activity. The estimated BCFs based only on the parent compounds were 675 and 490, respectively. Thus, biotransformation of the parent compounds occurred in addition to bioconcentration. Biotransformation by the mixed function oxidase system in the fish liver can result in the formation of carcinogenic and mutagenic intermediates; exposure to PAHs has been linked to the development of tumors in fish (Eisler 1987). The ability of fish to metabolize PAHs may explain why benzo(a)pyrene is frequently not detected or found at only very low levels in fish from environments heavily contaminated with PAHs (Varanasi and Gmur 1980, 1981). The breakdown products (polyhydroxy compounds) are eliminated in feces (via bile) and urine. Varanasi et al. (1985) ranked the amount of benzo(a)pyrene metabolism by aquatic organisms as follows: fish > shrimp > amphipod crustaceans > clams. Half lives for elimination of PAHs in fish ranged from less than 2 days to 9 days (Niimi 1987).

Molluscs also eliminate accumulated PAHs. Neff (1982) reported that oysters (Crassostrea gigas) eliminated the following percentages of accumulated PAHs during a 7-day elimination period: Benzo(a)pyrene--0%; benz(a)anthracene--32%; fluoranthene--66%, and anthracene--79%.

Fish and crustaceans readily assimilate PAHs from contaminated food, whereas assimilation in molluscs and polychaete worms is limited (Eisler 1987). Biomagnification (a systematic increase in tissue concentrations moving up a food chain) has not been reported because of the tendency of many aquatic organisms to eliminate these compounds rapidly (Eisler 1987). In general, PAHs obtained from the diet can contribute to total tissue concentrations to a limited extent. For example, food chain uptake of anthracene by fathead minnows (Pimephales promelas) consuming water fleas (Daphnia pulex) was estimated to be about 15% of the amount accumulated from the water (Southworth 1979).

Sediment-associated PAHs can be accumulated by bottom-dwelling invertebrates and fish (Eisler 1987). For example, Great Lakes sediments containing elevated levels of PAHs were reported by Eadie et al. (1983) to be the source of the body burdens of the compounds in bottom-dwelling invertebrates. Varanasi et al. (1985) found that benzo(a)pyrene was accumulated in fish, amphipod crustaceans, shrimp, and clams when estuarine sediment was the source of the compound. Approximate tissue to sediment ratios were 0.6-1.2 for amphipods, 0.1 for clams, and 0.05 for fish and shrimp.

PAHs can accumulate in terrestrial plants. Some terrestrial plants can take up PAHs via the roots or foliage; uptake rates are dependent on the concentration, solubility, and molecular weight of the PAH and on the plant species (Edwards 1983). Ratios of PAH concentrations in vegetation to those in soil ranged from 0.001 to 0.18 for total PAHs and from 0.002 to 0.33 for benzo(a)pyrene. About 30%-70% of atmospheric PAHs (indeno(1,2,3-cd)pyrene, fluoranthene, and benzo(a)pyrene) deposited on a forest were sorbed onto tree foliage (i.e., leaves and needles) and then deposited as litterfall (Matzner 1984). Vaughan (1984) stated that atmospheric deposition on leaves often greatly exceeds uptake from soil by roots as a route of PAH accumulation. Mosses and lichens have also been used to monitor atmospheric deposition of PAHs (Thomas et al. 1984).

PAHs may accumulate in terrestrial animals through the food chain or by ingestion of soil. The environmental fate of creosote coal tar distillate (which contained 21% phenanthrene and 9% acenaphthene) was studied in a terrestrial microcosm containing soil, rye grass, insects, snails, mealworm larvae, and earthworms by Gile et al. (1982). Two gray-tailed voles (Microtus canicaudus) were added 54 days after the start of the experiment, which continued for 19-26 more days. Average surface soil concentrations (measured on an unspecified day) were 0.60 ppm (phenanthrene) and 1.19 ppm (acenaphthene). During the last 3 days of the experiment, the following phenanthrene concentrations were measured: snail--3.27 ppm; pill bugs--1.72 ppm; and earthworm--18.30 ppm. The acenaphthene concentrations measured were: snail--11.2 ppm (day 37); pill bugs--0.99 ppm (day 75); and earthworm--71.9 ppm (day 72-75). The whole body concentration in the vole analyzed for phenanthrene was 7.20 ppm; in the vole analyzed for acenaphthene it was 37.00 ppm. The authors found that these compounds were not metabolized in this system. Concentrations in the vole exceeded soil concentrations by a factor of 12 for phenanthrene and 31 for acenaphthene.

5.3.2 Transformation and Degradation

5.3.2.1 Air

PAHs can undergo photooxidation and can react in the atmosphere with pollutants such as ozone, nitrogen oxides, sulfur dioxide, and peroxyacetylnitrate (NRC 1983). Atmospheric half lives are generally less than 30 days. Reaction with ozone or peroxyacetylnitrate yields diones; nitrogen oxide reactions yield nitro and dinitro PAHs. Sulfonic acids have also been formed from reaction with sulfur dioxide.

Photochemical oxidation of a number of PAHs has been reported (EPA 1988a), with the formation of nitrated PAHs, quinones, phenols, and dihydrodiols (Kamens et al. 1986; Holloway et al. 1987). Some of these breakdown products are mutagenic (Gibson et al. 1978). The National Research Council (NRC 1983) noted that compounds adsorbed to soot are more resistant to photochemical reactions than pure compounds. Butler and Crossley (1981) estimated half-lives for degradation of the following PAHs adsorbed to soot particles and exposed to sunlight in air containing 10 ppm nitrogen oxides: Benzo(a)pyrene--7 days; benzo(ghi)perylene--8 days; benz(a)anthracene--11 days; pyrene--14 days; chrysene--26 days; fluoranthene--27 days; and phenanthrene--30 days. However, Thomas et al. (1968) reported that benzo(a)pyrene adsorbed on soot was readily photooxidized, with 60% of the compound destroyed within the first 40 minutes of exposure to sunlight. Eisenberg and Cunningham (1985) found that the photochemical reaction products of PAHs (anthracene, phenanthrene, fluoranthene, benz(a)anthracene, chrysene, and benzo(a)pyrene) adsorbed on particulates include singlet oxygen, which may be implicated in the formation of mutagenic compounds.

Some PAHs are degraded by oxidation reactions that have been measured in the dark (to eliminate the possibility of photodegradation). Korfmacher et al. (1980) found that, while fluorene was completely oxidized, fluoranthene and phenanthrene were not oxidized and benzo(a)pyrene and anthracene underwent minimal oxidation. These compounds were tested adsorbed to coal fly ash; the authors stated that the form of the compound (adsorbed or pure) and the nature of the adsorbent greatly affect the rate and extent of this process.

5.3.2.2 Water

The most important processes contributing to the degradation of PAHs in water are photooxidation, chemical oxidation, and biodegradation by aquatic microorganisms (Neff 1979). Hydrolysis is not considered to be an important degradation process for PAHs (Radding et al. 1976). In natural aquatic systems, photooxidation and biodegradation can significantly contribute to the degradation of PAHs, depending on environmental conditions.

The rate and extent of photodegradation varies widely among the PAHs (Neff 1979). Factors such as water depth, turbidity, and temperature affect the rate of photodegradation. In the photooxidation of PAHs, the most common reactions result in the formation of peroxides, quinones, and diones (NAS 1972). A study by Nagata and Kondo (1977) reported that anthracene, phenanthrene, and benz(a)anthracene were susceptible to photodegradation, and that benzo(a)pyrene, chrysene, fluorene, and pyrene were resistant to photodegradation.

PAHs in water can be chemically oxidized by chlorination and ozonation. A high efficiency of degradation of PAHs from chlorination has been reported by Harrison et al. (1976a, 1976b) for both laboratory and waste water treatment plant conditions. Pyrene was the most rapidly degraded PAH. Benz(a)anthracene, benzo(a)pyrene, and perylene were also highly degraded. Indeno(1,2,3-cd)pyrene and benzo(ghi)pyrene were intermediate in relative degradation. Benzo(k)fluoranthene and fluoranthene were the most slowly degraded of the compounds tested.

The PAH-related byproducts resulting from chlorination are not fully known (Neff 1979). Oyler et al. (1978) identified the following products resulting from the chlorination of PAHs: anthraquinone, a chlorohydrin of fluoranthene, monochloro derivatives of fluorene, phenanthrene, 1-methylphenanthrene, and 1-methylnaphthalene.

In water, ozonation is generally slower and less efficient than chlorination in degrading PAHs (Neff 1979). Reaction pathways for ozonation of some PAHs include: benz(a)anthracene to 7,12-quinone; benzo(a)pyrene to 3,6-, 1,6-, and 4,5-diones; and fluorene to fluorenone (NAS 1972).

In general, PAHs can be significantly metabolized by microbes under oxygenated conditions. However, under anoxic conditions, degradation will be extremely slow (Neff 1979). Some PAHs are partially or completely degraded by some species of aquatic bacteria and fungi. Initial reactions generally involve the introduction of two hydroxyl groups into the aromatic nucleus resulting in the formation of a dihydrodiol intermediate (Neff 1979). The bacterial degradation pathway includes the formation of cis-dihydrodiol via a dioxetane intermediate, whereas in fungi and mammalian systems (which, unlike bacteria, both have cytochrome P-450 enzyme systems), trans-dihydrodiol is produced via an arene oxide intermediate (Neff 1979). This is significant since the arene oxides have been linked to the carcinogenicity of PAHs.

Algae were found to transform benzo(a)pyrene to oxides, peroxides, and dihydrodiols (Kirso et al. 1983; Warshawsky et al. 1983). Microorganisms in stored groundwater samples completely degraded acenaphthene and acenaphthylene within 3 days (Ogawa et al. 1982). Whereas these reactions occurred under aerobic conditions, there was no evidence of anaerobic degradation of PAHs within the aquifer from which the samples were obtained.

Information on the biodegradation of PAHs by fungi is limited compared to the information available for bacteria. While no information was found on the 15 PAHs discussed in this document, the fungus Cunninghamella elegans has been reported to be capable of metabolizing naphthalene (Cerniglia and Gibson 1979).

5.3.2.3 Soil

Microbial metabolism is the major process for degradation of PAHs in soil environments. Photolysis, hydrolysis, and oxidation are not considered important processes for the degradation of PAHs in soils (Sims and Overcash 1983). The rate and extent of degradation of PAHs in soil are affected by environmental factors, characteristics of the microbial population, and the physical and chemical properties of the PAHs. Environmental factors that may influence the rate of PAH degradation in soil include temperature, pH, oxygen concentration, PAH concentrations and contamination history of soil, soil type, moisture, nutrients, and other substances that may act as substrate co-metabolites (Sims and Overcash 1983). The size and composition of microbial populations can in turn be affected by these factors. For example, in low pH soils, fungi are dominant over bacteria, and thereby control microbial degradation in these environments.

While the pathways of microbial degradation are well known for anthracene, benzo(a)pyrene, and phenanthrene, degradation pathways for other PAHs are largely unknown (Sims and Overcash 1983). Metabolism of PAHs by bacteria includes the formation of cis-dihydrodiols through dioxetane intermediates, whereas in fungi (and mammalian systems) trans-dihydrodiols are produced through arene oxide intermediates (Sims and Overcash 1983). This is significant because arene oxides have been linked to the carcinogenicity of PAHs. The initial reaction products of PAH microbial degradation are further degraded to catechol, protocatechuic acid, and gentisic acid. These compounds are then degraded to acetic, fumaric, pyruvic, and succinic acid, and acetaldehyde.

Anthracene and fluoranthene showed slightly higher biodegradation rates than benz(a)anthracene or benzo(a)pyrene in a study with fine and medium sands and marsh sediments (Gardner et al. 1979). Degradation rates expressed as percentage of the mass removed per week for the four compounds were anthracene 2.0%-3.0%, fluoranthene 1.9%-2.4%, benz(a)anthracene 1.4%-1.8%, and benzo(a)pyrene 0.84%-1.4%.

The rate of biodegradation may be altered by the degree of contamination. Benzo(a)pyrene in a previously uncontaminated soil was reduced by soil microorganisms by 33% after 3 months (Ya Khesina et al. 1969). Benzo(a)pyrene was reduced by 71% in a moderately oil-contaminated soil, and 52% in a highly oil-contaminated soil. At hazardous waste sites, half-lives may be longer since other contaminants at the site may be toxic to degrading microorganisms. Bossert and Bartha (1986) reported reduced biodegradation of PAHs in soil containing a chemical toxic to microorganisms.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

PAHs are widely distributed in the environment and have been detected in air, water, sediment, soil, food and other consumer products.

5.4.1 Air

Some data are available which suggest higher concentrations of PAHs in urban air versus rural. Pucknat (1981) summarized 1970 data from the U.S. National Air Surveillance Network and reported that benzo(a)pyrene concentrations in 120 U.S. cities were between 0.2 and 19.3 ng/m^3. Ambient benzo(a)pyrene concentrations in nonurban areas ranged between 0.1 and 1.2 ng/m^3. More recently, Greenberg et al. (1985) studied PAH levels in New Jersey over two summer and winter seasons and found that urban areas had PAH levels approximately 3 to 5 times higher than those in a rural site. Geometric mean concentrations of 8 PAHs (benzo(a)pyrene, benzo(b)fluoranthene, benzo(k)fluoranthene, benz(a)anthracene, indeno(1,2,3-cd)pyrene, chrysene, benzo(ghi)perylene, and pyrene) ranged from 0.15 to 0.62 ng/m^3 in urban areas and from 0.02 to 0.12 ng/m^3 in rural areas.

In a study that characterized air levels for a variety of PAHs, Gordon (1976) reported median ambient levels of individual PAHs in Los Angeles ranging from 0.18 ng/m^3 for benz(a)anthracene to 3.27 ng/m^3 for benzo(ghi)perylene. Most individual PAHs had a median concentration of less than 0.6 ng/m^3. The relatively high levels of benzo(ghi)perylene were probably related to high levels of automobile emissions, which are known to contain high levels of benzo(ghi)perylene relative to other PAHs (Santodonato 1981). During the same time period, Fox and Stanley (1976) reported average concentrations of PAH in the range of 3.2 ng/m^3 for benzo(a)pyrene to 5.2 ng/m^3 for pyrene. Much higher concentrations were reported in the Baltimore Harbor Tunnel where the average concentrations of individual PAHs ranged from 66 ng/m^3 for benzo(a)pyrene to 120 ng/m^3 for pyrene.

Certain monitoring data suggest that ambient levels of some PAHs may be decreasing. Faoro and Manning (1981) analyzed a limited sample of U.S. National Air Surveillance Network data updated through 1977, which indicated that benzo(a)pyrene concentrations have shown consistent, sizeable declines during the period from 1967 to 1977 at 26 urban sites and 3 background sites studied (data not provided). Although data from studies in different areas cannot be used to indicate definitive temporal trends in PAH air levels, a comparison of PAH levels in urban areas from the Gordon (1976) study and the Greenberg et al. (1985) study suggests that the levels of other PAHs may also be decreasing.

5.4.2 Water

PAHs have been detected in surface waters of the United States. Basu and Saxena (1978a) reported concentrations of selected PAHs in surface waters used as drinking water sources in four U.S. cities (Huntington, West Virginia; Buffalo, New York; and Pittsburgh and Philadelphia, Pennsylvania). Total concentrations of PAHs ranged from 4.7 ng/L in Buffalo to 600 ng/L in Pittsburgh.

More recently, DeLeon et al. (1986) analyzed surface water from 11 locations in the Mississippi River. Seventeen PAHs were identified in the samples at levels ranging from 1 ng/L for six compounds to a high of 34 ng/L for phenanthrene. The highest concentration of phenanthrene was detected in a sample collected near New Orleans, Louisiana, near an industrial area, implicating industrial effluent or surface water runoff from this area as a possible source.

PAHs have been detected in urban runoff generally at concentrations much higher than those reported for surface water. Data collected as part of the Nationwide Urban Runoff Program indicate concentrations of individual PAHs in the range of 300 to 10,000 ng/L, with the concentrations of most PAHs above 1,000 ng/L (Cole et al. 1984). Industrial effluents also have elevated PAHs levels. Morselli and Zappoli (1988) reported similarly elevated PAH levels in refinery waste waters, with concentrations for most PAHs in the range of 400 ng/L (benzo(b)fluoranthene) to 16,000 ng/L (phenanthrene).

PAHs have also been detected in sediments, generally at concentrations higher than those detected in surface water (i.e., in the range of parts per billion rather than parts per trillion). Eadie et al. (1982) analyzed surficial sediments in southwestern Lake Erie near a large coal-fired power plant. Sediment concentrations for total PAHs were generally in the range of 530 to 700 μg/kg, although concentrations in river and near-shore sediments reached nearly 4,000 μg/kg (4 ppm). Heit et al. (1981) reported concentrations of PAH (3 to 7 ring PAH) from two lakes in the Adirondack acid lake region totalling 2,660 μg/kg and 770 μg/kg (calculated from data presented). Concentrations of PAHs in sediments from Cape Cod and Buzzards

Bay in Massachusetts and the gulf of Maine have been reported to be in the range of 540 to 1,300 ppb (Hites et al. 1980).

Few data are available on the concentrations of PAHs in U.S. groundwater. Basu and Saxena (1978b) reported total PAH concentrations in groundwater from three sites in Illinois, Indiana, and Ohio to be in the range of 3 to 20 ng/L. Data summarized by Sorrel et al. (1980) indicate low levels of PAHs in finished drinking waters of the United States. Reported maximum concentrations for total PAHs (based on measurement of 15 PAHs) in the drinking water of 10 cities ranged from 4 ng/L to 24 ng/L. The low concentrations of PAHs in finished drinking water were attributed to efficient water treatment processes; concentrations in untreated water ranged from 6 ng/liter to 125 ng/L.

5.4.3 Soil

PAHs are ubiquitous in soil. Background concentrations for rural, agricultural, and urban soils (from the U.S. and other countries) are given in Table 5-5. In general, concentrations ranked as follows: urban > agricultural > rural. Evidence of the global distribution of PAHs was given by Thomas (1986) who detected benzo(ghi)perylene and fluoranthene at concentrations above 150 μg/kg in arctic soils. Soil samples collected from remote wooded areas of Wyoming contained total PAH concentrations of up to 210 μg/kg. Total PAH concentrations of 4,000-8,000 μg/kg were found in the soil near a complex road interchange in Switzerland while a level of 2,300 μg/kg was measured in an area removed from the road. A concentration of 650,000 μg/kg benzo(a)pyrene was measured in soil 10 meters from an industrial plant in Germany (Edwards 1983).

5.4.4 Other Environmental Media

PAHs are present at 1 to 2 weight % in crude oils. The compounds are also found in refined petroleum products including gasoline, kerosene, diesel fuel, some heating oils, and motor oil (Guerin 1978).

PAHs have also been detected in used motor oils. The following concentrations of benzo(a)pyrene and benz(a)anthracene measured in 1,071 samples of used motor oils were reported by Franklin Associates (1984):

	Positive Samples (%)	Mean (ppm)	Median (ppm)	Range (ppm)
Benzo(a)pyrene	58	24.5	10	<1 - 405
Benz(a)anthracene	74	71.3	12	<5 - 660

PAHs have been detected in unprocessed cereal, potatoes, grain, flour, bread, vegetables, and fruits. The concentrations in uncooked foods largely depend on the source of the food. For example, vegetables and fruits obtained from a polluted environment may contain higher PAH concentrations than those

TABLE 5-5. Background Soil Concentrations of Polycyclic Aromatic Hydrocarbons (PAHs)

	Concentration (μg/kg)		
Compound	Rural Soil	Agricultural Soil	Urban Soil
Acenaphthene	1.7	6	
Acenaphthylene		5	
Anthracene		11-13	
Benzo(a)anthracene	5-20	56-110	169-59,000
Benzo(a)pyrene	2-1,300	4.6-900	165-220
Benzo(b)fluoranthene	20-30	58-220	15,000-62,000
Benzo(e)pyrene		53-130	60-14,000
Benzo(ghi)perylene	10-70	66	900-47,000
Benzo(k)fluoranthene	10-110	58-250	300-26,000
Chrysene	38.3	78-120	251-640
Fluoranthene	0.3-40	120-210	200-166,000
Fluorene		9.7	
Indeno(1,2,3-cd)pyrene	10-15	63-100	8,000-61,000
Phenanthrene	30.0	48-140	
Pyrene	1-19.7	99-150	145-147,000

Sources:
IARC (1973)
White and Vanderslice (1980)
Windsor and Hites (1979)
Edwards (1983)
Butler et al. (1984)
Vogt et al. (1987)
Jones et al. (1987)

obtained from nonpolluted environments. Benzo(a)pyrene, dibenz(a,h)anthracene, and chrysene have been detected in vegetables grown near a heavily traveled road (Wang and Meresz 1982). The method of cooking can also influence the PAH content of food; the time of cooking, the distance from the heat source, and the drainage of fat during cooking (e.g., cooking in a pan versus on a grill) all influence PAH content. For example, charcoal broiling increases the amount of PAHs in meat.

The following ranges of benzo(a)pyrene concentration (wet or dry weight not specified) were summarized by Santodonato et al. (1981) from studies conducted in many countries:

- cooking oils--0.5-8 ppm
- margarine--0.2-6.8 ppm
- smoked fish--trace-6.6 ppm
- smoked or broiled meats--trace-10.5 ppm
- grains and cereals--not detected-60 ppm
- fruits--not detected-29.7 ppm
- vegetables--not detected-24.3 ppm

These data include samples from areas identified as "polluted." Edwards (1983) stated that the maximum total concentrations of PAHs in vegetation near a source was 25,000 ppb (dry weight), while concentrations in non-source areas ranged from 20 to 1,000 ppb. In general, concentrations in leaves, stems, and fruits were higher than those in roots. Edwards (1983) reported that washing removed a maximum of 25% of PAHs on the leaves of plants. In a composite sample characterized to be typical of the U.S. diet, Howard (1979) found that PAH concentrations in all food groups were less than 2 ppb.

PAHs have also been reported to occur in chewing tobacco, snuff, and in mainstream and sidestream tobacco smoke. Concentrations of benzo(a)pyrene in cigarette mainstream smoke between 5 and 78 ng/cigarette have been reported (IARC 1983). Concentrations in sidestream smoke have been reported to be even higher (Adams et al. 1987). In snuff, benzo(a)pyrene concentrations of 0.42-63 ppb have been reported (Brunnemann et al. 1986).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The greatest sources of exposure to PAHs for most of the U.S. population are active or passive inhalation of the compounds in tobacco smoke, wood smoke, and contaminated air, and ingestion of the compounds in foodstuffs. Smoking has been estimated to result in exposure to benzo(a)pyrene of 0.4 μg/day (Santodonato 1981). Other potential routes of human exposure are ingestion of contaminated drinking water and food products, and skin contact with soot and tars. PAHs are ubiquitous in the environment, resulting from the incomplete combustion of organic materials, whether natural (forest fires or volcanoes) or man-made (combustion of fuels for heating and transportation). The amount of PAHs found in food products depends as much on the method of preparation (especially grilling or smoking) as on the origin of the food. Disinfection of public water supplies with chlorine can result in the presence of chlorinated and oxygen substituted PAHs (Shiraishi et al. 1985). Coal tar preparations have been used in the clinical treatment of skin disorders. Contamination of the ambient air can be derived from industrial and construction sources. Eldridge et al. (1983) measured substantial levels of PAHs emitted from freshly laid petroleum road asphalt.

Estimates of general population exposure to total PAHs (μg/day) and carcinogenic PAHs in comparison to readily measured benzo(a)pyrene concentrations were presented by Santodonato et al. (1981), as follows:

Source	Benzo(a)pyrene	Carcinogenic PAHs*	Total PAHs
Air	0.0095-0.0435	0.038	0.207
Water	0.0011	0.0042	0.027
Food	0.16-1.6	--	0.16-1.6

*Total of benzo(a)pyrene, benzo(j)fluoranthene, and indeno(1,2,3-cd)pyrene.

Lioy et al. (1988) conducted a multimedia study of human exposure to benzo(a)pyrene in a rural town in New Jersey where the major industry was a grey-iron pipe- manufacturing plant, which contributed to high levels of benzo(a)pyrene in the atmosphere. Benzo(a)pyrene levels in 10 homes were measured in the range of 0.1 to 8.1 ng/m^3, depending on personal habits (whether the windows were kept open, how frequently the doors were opened, cooking methods, hobbies, whether home improvements were being made) and sources of home heating. The mean outdoor air concentration of benzo(a)pyrene was 0.9 ng/m^3. In samples of food collected over a 2 week period, the maximum level of benzo(a)pyrene was 1 ng/g (wet weight). Ingestion of benzo(a)pyrene was estimated to be between 10 and 4,005 ng benzo(a)pyrene per individual per week. No detectable amounts of benzo(a)pyrene were observed in the drinking water supply (detection limit: 0.1 ng/L). In comparing the inhalation and ingestion pathways in each home, Lioy et al. (1988) found that potential intake could be similar in each medium. In about half of the cases (19 homes over a 2-week exposure period), higher food benzo(a)pyrene exposures were found. In the other 10 cases, high inhalation benzo(a)pyrene exposures were found. The range of food exposures was much greater than the range of air exposures.

Industrial exposure can result from processes such as the production of coke, the manufacture of anodes, and the production of aluminum. The use of coal tar, pitch, asphalt, creosote, soot, and anthracene oil is widespread in the manufacture of fuel, dyes, plastics, paints, insulating materials, impregnating materials, building materials, road-building materials, embedding material, rubber, inks, and brushes (Hueper 1949). Faulds et al. (1981) found that PAHs in diesel engine exhaust attach to respirable dust particles and travel long distances in underground mines, resulting in exposure of mine workers far removed from engine sites. Mechanics may also be exposed to PAHs resulting from the pyrolytic decomposition of the organic fractions of abraded particles from clutch and brake linings (Knecht et al. 1987).

The National Occupational Hazard Survey (NOHS), conducted by NIOSH from 1972 to 1974, estimated the number of workers potentially exposed to various chemicals in the workplace in 1970 (NIOSH 1976). These estimates are derived from direct observation of the use of the chemicals in trade name products. The data for the three PAHs included in the survey are summarized below:

Chemical	Number of Plants	Number of Workers
Acenaphthene	485	1,920
Fluoranthene	90	382
Pyrene	11	32

Preliminary data from a second workplace survey, the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1980 to 1983, estimated the number of workers potentially exposed to various chemicals in the workplace in 1980 (NIOSH 1984), including a separate tally of female workers. The data for the five PAHs included in the survey are summarized below:

Chemical	Number of Plants	Total Workers (Female Workers)	
Acenaphthene[a]	7	14	(0)
Anthracene[a]	7	21	(0)
Fluoranthene[b]	464	11,353	(1,770)
Fluorene[a]	70	1,862	(1,504)
Pyrene[a]	7	28	(0)

Neither the NOHS nor the NOES databases contains information on the frequency, level, or duration of exposure of workers to any of the chemicals listed. They provide only estimates of workers potentially exposed to the chemicals.

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[a] These estimates derived from direct observation of the use of the chemical.

[b] This estimate derived from direct observation of the use of the chemical in trade name products.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Human exposure to PAHs is expected to be highest among certain occupational groups (e.g., individuals working with coal tar and its products, foundry workers, miners, chimney sweeps), smokers and nonsmokers living or working in close proximity to smokers, members of the general population living in the vicinity of emission sources or using products containing PAHs, and persons living in the vicinity of NPL sites where PAHs have been detected above background levels. Persons who consume grilled or smoked food may ingest high levels of these compounds. Anyone who works extensively with products such as roofing materials, asphalt, and other PAH-containing substances may be exposed through inhalation or skin contact.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of PAHs is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of PAHs.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The chemical and physical properties of PAHs are well characterized and the data exist to permit estimations of their environmental fate. No additional data are needed at this time.

Production, Use, Release, and Disposal. Humans are at high risk of exposure to PAHs because of their widespread distribution in the air, water, and soil. Since most PAHs are produced by incomplete combustion of wood and fuels, and these sources vary widely over time, it is difficult to compare current production with past and potential future production. Only a few PAHs have commercial uses that might contribute to contamination of the environment. The widespread distribution of PAHs results primarily from their release to the atmosphere from natural and man-made sources, including emissions from volcanoes and forest fires, wood-burning stoves and furnaces, motor vehicles, trucks, and other gas-burning engines, and cigarette smoke. PAHs in the atmosphere are deposited to water and soil. Fruits and vegetables can become contaminated if they are grown in a contaminated environment or during cooking (e.g., charcoal broiled foods). The criteria for disposal practices are currently being revised. Information on the amounts disposed of by each method would be useful in determining the extent of risk to populations located near land disposal sites.

Environmental Fate. The environmental fate of PAHs is well characterized. PAHs are transported in, and partitioned to, the air, water, and soil. Transformation and degradation processes of PAHs in the air, water, and soil have been well studied. No additional information is needed.

Bioavailability from Environmental Media. PAHs can be absorbed following inhalation, oral, or dermal exposure. These routes of exposure may be of concern to humans because of the potential of PAHs to contaminate drinking water, food, and soil. Limited information is available regarding the bioavailability of PAHs from plants grown in contaminated soil. More information on the absorption of PAHs from air, soil, and plants grown in contaminated soil would be helpful in identifying the risk for populations living near hazardous waste sites.

Food Chain Bioaccumulation. PAHs can bioaccumulate in plants, aquatic organisms, and animals from intake of contaminated water, soil, and food. Extensive metabolism of the compounds by high-trophic-level consumers, including humans, has been demonstrated; therefore, food chain biomagnification of the compounds does not appear to be significant. No additional bioaccumulation data are needed.

Exposure Levels in Environmental Media. PAHs are widely distributed in the environment and have been detected in air, water, sediment, soil, and food. Additional monitoring data is needed to allow for characterization of the levels of the compounds to which humans are potentially exposed. Although some studies of background levels in different media have been conducted, additional site-specific concentration data for ambient air, particularly in the vicinity of hazardous waste sites, would be helpful in estimating exposure of the general population through inhalation of contaminated air.

Exposure Levels in Humans. Populations living in the vicinity of hazardous waste sites may be at greater risk of potential exposure to PAHs than the general population through inhalation, ingestion, and direct contact with contaminated media. PAHs have generally not been detected in surveys of human adipose tissue (e.g., National Human Adipose Tissue Survey) and other biological media, presumably because the compounds are fairly rapidly metabolized. A few exposure estimates for the general population have been made from inhalation of ambient air and ingestion of contaminated drinking water and food, but sparse monitoring data limit the reliability of these estimates. Relatively recent estimates of the size of the workforce exposed to a few of the PAHs [such as benzo(a)pyrene] are available from NIOSH.

However, monitoring data on workplace exposure levels are generally inadequate, partially because of the complexity of air emissions in terms of number of compounds detected. Collecting information on exposure levels in humans would be important to better define exposure estimates in the general population and workforce, and to examine the relationship between levels of PAHs in the environment, human tissue levels, and the subsequent development of health effects.

Exposure Registries. No exposure registries for PAHs were located. These compounds are not currently among the compounds for which a subregistry has been established in the National Exposure Registry. These compounds will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to these compounds.

5.7.2 On-going Studies

No information was found in the available literature regarding on-going studies evaluating the environmental fate and human exposure potentials of PAHs. Remedial investigation/feasibility studies being conducted at the 6-84 NPL sites where PAHs have been found should provide data on concentrations of the compounds in contaminated media in the vicinity of hazardous waste sites.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring PAHs in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify PAHs. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect PAHs in environmental samples are the methods approved by federal agencies such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by a trade association such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

The analytical methods used to quantify PAHs in biological and environmental samples are summarized below. Table 6-1 lists the applicable analytical methods used for determining PAHs in biological fluids and tissues, and Table 6-2 lists the methods used for determining PAHs in environmental samples.

6.1 BIOLOGICAL MATERIALS

Several analytical techniques have been used to determine trace levels of PAHs in biological materials. These include gas chromatography equipped with a flame ionization detection (GC/FID), gas chromatography coupled to a mass spectrometry (GC/MS), high-performance liquid chromatography (HPLC), thin-layer chromatography (TLC), and spectrofluoremetry (SF). Immunoassays, i.e., enzyme-linked immunosorbent assays (ELISA) and ultrasensitive enzyme radioimmunoassay (USERIA), ^{32}P-postlabeling, and synchronous luminescence spectroscopy (SLS) are methods currently being developed to detect the presence of carcinogenic PAH adducts bound covalently to macromolecules (e.g., DNA).

Recently, Liao et al. (1988) developed a relatively simple and rapid procedure for purifying human and bovine adipose tissue extracts so that trace levels of complex mixture of target analytes (including PAHs) could be detected and quantitated by capillary GC/MS. By employing an activated Florisil column, Liao and co-workers indicated that lipid contaminants bind effectively (more than 99.75%) with Florisil, thereby achieving a relatively clean sample extract. A detection limit at a low ng/g level and an average sample recovery of 85% were achieved (Gay et al. 1980; Liao et al. 1988; Modica et al. 1982).

TABLE 6-1. Analytical Methods for Determining PAHs in Biological Materials

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Biological tissues (adipose)	Add 8% benzene in hexane to adipose tissue sample and homogenize; clean-up on florisil column;	GC/MS	5-50 ng/g	52-95% recovery	Liao et al. 1988
	Extract with pentane; clean-up on florisil and silica column	GC/MS	0.05 ng/sample	27%-100% recovery	Gay et al. 1980
	Extract tissues with cyclohexane; load onto alumina column and elute with cyclohexane; concentrate eluent and analyze	GC/FID	50 ng/sample	83%-95% recovery	Modica et al. 1982
Lungs	Homogenize lung sample with hexane; add 25% DMSO in water and shake; separate hexane layer, wash with water, and concentrate	SF	No data	95% recovery	Mitchell 1979
	Treat sample with hot 4 M KOH; extract with cyclohexane, concentrate and silica gel column	TLC	ng/g range	No data	Tomingas et al. 1976
	Digest tissue and extract nucleic acid (DNA); precipitate DNA with spermine and hydrolyze DNA in 0.1 M HCl	HPLC	13.3-32.7 x10^{-15} mol BPDE bound/mg DNA	No data	Weyand and Bevan 1987a
Liver	Add S-9 mix to homogenized sample in DMSO and incubate with shaking at 37°C; extract with ethyl acetate; concentrate and analyze metabolites of indeno[1,2,3-cd]pyrene	HPLC	No data	No data	Rice et al. 1985b
	Same procedure as above (Rice et al. 1985) except benzo[b]fluoranthene metabolites were analyzed	HPLC	No data	No data	Amin et al. 1982
Liver	Homogenize sample, saponify and extract with hexane; clean-up on silica or alumina column	HPLC	0.006-0.46 ng/g range	No data	Obana et al. 1981
Skin	Digest PAH-treated skin tissue; deproteinize and extract DNA; precipitate DNA and hydrolyze sample with 1.2 M HCl	HPLC	10^{-15} mol BPDE per sample	No data	Shugart et al. 1983

TABLE 6-1 (Continued)

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Skin (Cont.)	Modify DNA content of PAH-treated skin tissue in vitro; label PAH-DNA adduct by ^{32}P-postlabeling technique and analyze	^{32}P-postlabeling followed by autoradiography and TLC	90-1,210 x10^{-15} mol PAH adduct per mg DNA	No data	Phillips et al. 1987
Blood	Hydrolyse BPDE-DNA adduct sample with 0.1 M HCl; analyze hydrolysis products (benzo[a]pyrene-tetrols and triols)	SLS	No data	No data	Haugen et al. 1986
	Treat sample with 2% horse serum; add rabbit anti-BPDE-DNA anti-serum to sample and incubate, add alkaline phosphatase-conjugated goat anti-rabbit IgG, PNPP and radiolabeled PNPP, $MgCl_2$ and incubate; separate hydrolyzed radiolabeled PNPP and measure radioactivity	USERIA	0.38-2.2 x10^{-15} mol per µg DNA	No data	Haugen et al. 1986
	Add BPDE-DNA adduct sample to goat anti-human IgG reagent, horseradish peroxidase and substrate solution and incubate	ELISA	0.38-2.2 x10^{-15} mol BPDE per µg DNA	No data	Haugen et al. 1986
	Separate white blood cells and isolate DNA by standard RNase and phenol treatment; assay BPDE-DNA adduct by immunoassay	ELISA	1x10^{-15} mol BPDE per 0.001 mg DNA (Perera et al. 1988) 2-120 x10^{-15} BPDE per 50 µg DNA (Shamsuddin et al. 1985)	No data	Perera et al. 1988; Shamsuddin et al. 1985
	Lysis the red blood cells and centrifuge to separate hemaglobin (hb); isolate BPDE-hb adduct by acid hydrolysis; clean-up on Sep-Pak and DEAE-cellulose column	HPLC	5x10^{-12} g BPDE per sample	No data	Shugart 1986
	Isolate PAH-DNA adduct from white blood cells of blood; digest adduct with [gamma ^{32}P] ATP; resolve the ^{32}P-labelled adduct on TLC plate and count radioactivity	TLC and Autoradiography	0.3x10^{-15} mols adduct per µg DNA	No data	Phillips et al. 1988

TABLE 6-1 (Continued)

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Blood (Cont.)	Collect lymphocyte cells and isolate BPDE-DNA adduct by standard treatment; assay BPDE-DNA adduct by immuno assay and analyses by SLS	ELISA or USERIA and SLS	0.06 to 0.23×10^{-15} mol BPDE/ μg DNA	No data	Harris et al. 1985
Feces	Extract sample with benzene: MeOH (4:1); add MeOH:H_2O (4:1) clean-up on silica gel column	HPLC	0.05 μg/g	No data	Hecht et al. 1979
Urine	Adjust urine sample to pH 3 with HCl and clean-up on activated Sep-Pak C18 cartridge column; reduce extract with hydriodic acid	HPLC	<1 μg PAH per mmol creatinine	10%-85% accuracy	Becher and Bjorseth 1983
	Extract urine sample with cyclohexane and concentrate; reduce sample with hot acid and analyze	GC/FID	1.2 to 6.48 μg PAH per mmol creatinine	No data	Becher and Bjorseth 1985
	Load urine sample onto a Sep-Pak column, wash with water followed by 10% MeOH; elute with 100% MeOH, concentrate, add 0.1M HCL, heat and analyze	SLS	25 pg metabolite per ml	No data	Uziel et al. 1987
Urine	Inject animal with radiolabelled benzo(a)pyrene; collect urine sample, add MeOH and load onto C-18 Sep-Pak column; elute with aqueous MeOH	HPLC	5×10^{-12} mol 7-BPDE-Gua per 10 μg of labelled Benzo(a)-pyrene	No data	Autrup and Seremet 1986

GC/MS = gas chromatography/mass spectrometry; GC/FID = gas chromatography/flame ionization detector; SF = spectrofluorometer; TLC = thin-layer chromatography; HPLC = high performance liquid chromatography; SLS = synchronous luminescence spectroscopy; USERIA = ultra sensitive enzyme radioimmuno assay; ELISA - enzyme linked immunosorbent assay; $NADP^+$ = oxidized nicotinamide adenosine dinucleotide; DMSO = dimethyl sulfoxide; BPDE = 7β, 8α-dihydroxy-(9α, 10α)-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene; Gua = Guanosine; B(a)P - benzo(a)pyrene; PNPP - para nitrophenyl phosphate; IgG = immunoglobulin; PAHs = polycyclic aromatic hydrocarbons.

TABLE 6-2. Analytical Methods for Determining PAHs in Environmental Samples

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Air	Pump gas and particulate matter from workplace through glass-fiber filter-amberlite XAD-2 adsorbent sampling system; extract ultrasonically with diethyl ether	HPLC	5-2,500 ppm	87%-100% recovery	Andersson et al. 1983
	Collect air sample through glass-fiber filter in a sampling train; extract filter with dichloromethane, clean-up on silica gel column; analyze at 254 nm	GC/DAD	0.2-4.8 ng per sample	75%-100% recovery	Desilets et al. 1984
	Collect air particulate matter on glass-fiber filter; extract filter with benzene:MeOH (4:1), concentrate extract dryness; separate residue by extraction into acid/neutral/base fractions; analyze neutral fraction for PAH	GC/FID and HPLC	0.00005 ppm	<8% RSD	Matsumoto and Kashimoto 1985
	Collect air sample from graphite electrode plant on a glass-fiber filter; insert filter into oven of GC and thermally desorb	GC/LIMF	1-15 μg per sample	±25% RSD	Galle and Grennfelt 1983
	Collect air particulates on glass-fiber filter; extract sample with 35% methylene chloride in cyclohexane	HPLC	<0.01 ng per sample	±2.5% RSD	Golden and Sawicki 1978
	Collect sample through filter; extract filter with organic solvent	TLC and GC/MS	<1 pg per sample	No data	Majer et al. 1970
	Collect sample through fiber-glass filter; extract filter with cyclohexane and concentrate	GC/GPFD	$1x10^{-6}$ ppm	±2.3% RSD	Mulik et al. 1975
	Collect air sample from woodburning furnace and extract with toluene; add 10 5 NaOH and shake; acidify organic layer; dry and concentrate	HPLC and GC/MS	0.11 ppm	>85% recovery	Naikwadi et al. 1987
	Collect air borne particulates from coal gasifier on glass-fiber filter; extract filter with benzene, concentrate	HPLC	<0.001 ppm	8%-100% recovery	Tomkins et al. 1982
	Collect sample on filter and extract with cyclohexane; purify crude PAH by eluting through silica column	GC/MS	0.001-0.002 ppm	4%-9% RSD	Oehme 1983

TABLE 6-2 (Continued)

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Air (Cont.)	Collect sample on glass-fiber filter or XAD-2 resin tube and extract with benzene or methylene chloride	HPLC and GC/MS	0.001-0.1 ppm	No data	Harvath 1983
	Collect air particulates on glass-fiber filter; extract filter with benzene and concentrate	HPLC	0.000025 ppm	92%-100% recovery	Fox and Stanley 1976
	Collect sample on filter and extract with benzene	TLC and SP	0.9-100 ppm	No data	Kertesz-Saringer and Morlin 1975
	Collect sample through filter or XAD-2 resin; extract with benzene, cyclohexane or methylene chloride	HPLC or GC/FID	<1 ppm	No data	NIOSH 1984 (Methods 5506 and 5515)
	Collect air particulate on XAD-2 resin; extract with and concentrate	RTP and SLS	No data	No data	Vo-Dinh 1981
	Collect air sample around refinery on a glass-fiber filter; extract with cyclohexane and the DMSO:Pentane (1:1)	GC/MS	0.00001 ppm	No data	Karlesky et al. 1987
Water	Extract sea water sample with hexane or carbon tetrachloride; separate hydrocarbons in IM H_2SO_4 followed by IM NaOH; clean-up extracts on silica and alumina columns	GC/FID	0.024-0.045 µg/L	44%-85% recovery	Desiderie et al. 1984
	Pass tap water sample through column containing XAD-4:XAD-8 (1:1) resin, extract sample by eluting resin with acetone followed by chloroform	HPLC and GC/MS	0.01-3 µg/L	No data	Thruston 1978
	Extract lake water with cyclohexane	HPLC with time-resolved fluorescence detection	180×10^{-15} g per sample	3.9% precision	Furuta and Otsuki 1983
	Extract sample at neutral pH with methylene chloride	HPLC, GC/FID or GC/MS	0.64-0.013 µg/L (HPLC) 2.0-45.1 µg/L (GC/FID) 1.9-7.8 µg/L (GC/MS)	No data	EPA 1986 (Methods 8100, 8250, and 8310)
Water (Cont.)	Pass tap water through sampling cartridges containing amberlite XAD-2 resin; extract PAH from resin by eluting with acetone:hexane (15:85)	GC/MS	0.00005 µg/L	57%-100% recovery	Beniot et al. 1979

TABLE 6-2 (Continued)

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Sediments	Extract sample with methylene chloride and clean-up on alumina column	TLC and GC/MS	0.2-2.7 µg/g	86%-89% recovery	John and Nickless 1977
	Freeze dry, sieve and homogenize sample; extract with dichloromethane (DCM) and clean-up on silica gel followed by sephadex column	HPLC/DAD/MS	pg range	No data	Quilliam and Sim 1988
	Dry sediment sample; add sample to methylene chloride and shake; inject extract in supercritical fluid extracting system	GC/MS	2.8-7.3 µg/g	91%-97% recovery	Hawthorne and Miller 1987a and b
	Dry sediment sample and extract with benzene and clean-up on silica gel and alumina column	GC/FID and GC/MS	0.014-0.093 µg/g	76%-110% recovery	Szepesy et al. 1981
Soil	Extract soil sample in organic solvent, concentrate and analyze	GC/FT-IR	0.025-0.25 µg per sample	0.998-0.850 correlation coefficient	Gurka and Pyle 1988
	Filter sample by sieving and extract ultrasonically with acetonitrile; pass extract through teflon filter and inject in HPLC	HPLC	0.017 µg/g	No data	Tanaka and Saito 1988
Sediments/ and suspended matter (river), airborne particulate, dust and soil	Dry wet sample in air and extract with methylene chloride; clean-up extract on activated copper column followed by sephadex	GC/FID and GC/MS	0.03-0.09 µg/g	99%-113% recovery	Giger and Schaffner 1978
Diesel exhaust particulate and dust	Collect sample on fiber filter; extract filter with hexane and concentrate; partition extract with DMSO and concentrate organic extract	HPTLC and FSD	1-50 pg per sample	±3% RSD	Butler et al. 1984
Waste water and sediments	Freeze dry sample and extract with chloroform:MeOH (2:1); concentrate crude extract and apply on TLC plate followed HPLC as clean-up procedures	GC/FID	0.12-0.46 µg/g	51%-100% recovery	Readman et al. 1986
Water and sediments	Extract sample in organic solvent	GC/FT-IR	0.01-0.06 µg/g	No data	Gurka et al. 1987

TABLE 6-2 (Continued)

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Cigarette smoke	Collect sample in the trapping system of smoking machine; dissolve sample in benzene:MeOH:H_2O (2:1:2); clean-up sample on silicic acid and gel filtration column	GC/FID	No data	92%-95% recovery	Severson et al. 1976
	Collect sample on filter pad; extract filter with cyclohexane	HPLC	3 pg/sample	89%-108% recovery	Risner 1988
Coal-fly ash	Dry sample in oven at 150°C and cool in desiccator; extract ultrasonically with methylene chloride and concentrate	GC/MS	No data	No data	Low et al. 1986
Coal-tar leachate	Extract sample with organic solvent using XAD-4 resin	GC/MS	No data	No data	Alben 1980
Highly refined coal-and petroleum-derived fuels	Dissolve sample in dichloromethane and inject into HPLC	HPLC/HPLC	3.5-46 µg/L	56%-100% recovery	Tomkins and Griest 1987
	Collect sample in brown Winchester bag; add 20% aqueous MeOH and shake; clean-up sample on Sep-Pak C-18 cartridge column	HPLC	0.1-7.1 µg/L	45%-95% recovery	Symons and Crick 1983
	Dissolve sample in hexane; clean-up on silica and alumina gel column	TLCV and SP	µg/L range	No data	Monarca and Fagicli 1981
	Dissolve sample in methylene chloride and analyze	HPLC and GC/MS	2000 µg/L	No data	Tomkins et al. 1986
Shale and fuel oil	Dissolve sample cyclohexane and partition sequentially with 1.5 M NaOH and IM HCl; clean-up neutral (PAH) fraction on alumina followed by alumina-silica column	XEOL	10 ng per sample	±5% RSD	Woo et al. 1980
	Dilute sample in ethanol and analyze	RTP and SLS	No data	RTP=±15% RSD; SLS=±5% RSD	Vo-Dinh et al. 1984
Sun tan oil	Extract sample with hexane and clean-up extract on silica gel column	TLC and SF	Low µg/L	79%-93% recovery	Monarca et al. 1982
White petroleum products	Load sample on silica gel column, elute column with pentane:ether (1.5:1) and concentrate eluent; clean-up on basic and acidic alumina column	FPS	µg/L range	No data	Popl et al. 1975

TABLE 6-2 (Continued)

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Sewage sludge	Homogenize sludge sample extract with cyclohexane; centrifuge, separate organic phase and concentrate	2-Dimensional TLC	<1 µg/g	80%-100% recovery	McIntyre et al. 1981
Smoked foods (e.g., fish and meet)	Saponify sample; extract with cyclohexane and clena-up on florisil column	HPLC, GC/FID and GC/MS	2-27 pg/ sample (HPLC) 10 pg/ sample (GC/FID 1,000 pg/kg (GC/MS)	28%-142% recovery	Lawrence and Weber 1984
	Homogenize sample in EtOH and solid KOH and extract with H_2O:TCTFE:EtOH (50:22:28); separate TCTFE layer, and clean-up on silica gel and alumina column	LC	0.1-6 ng/g	65%-107% recovery	Joe et al. 1984
Charcoal-broiled beef	Ground beef sample and extract with benzene:MeOH (4:1); evaporate extract to dryness and dissolve residue in MeOH:H_2O (4:1) and clean-up on silica gel column	HPLC	20-50 ng/g	No data	Hecht et al. 1979
Plants and humus	Extract sample with acetone; load extract onto alumina or silica gel column for clean-up; elute with organic solvent and concentrate eluent	HPTLC	ng/g range	No data	Thomas et al. 1984
Barley malt	Homogenize sample extract (ultrasonically) with cyclohexane; centrifuge, decant extract and clean-up on silica gel-alumina column	HPLC	2.5-5 ng/g	78%-97% recovery	Joe et al. 1982
Alcoholic beverage	Continuously extract sample with cyclohexane for 20 hr	HPLC and GC/FID	1 µg/L	60% recovery	Toussaint and Walker 1979
Tea	Saponify sample and extract with hexane, add DMSO and shake; clean-up extract on silica gel	TLC and FSD	2-12 ng/g	92%-95% recovery	Poole et al. 1987
Fish tissue	Homogenize sample with 1.15% KCl solution; load sample onto extract cartridges packed with a styrene-divinylbenzene copolymer resin; wash sample with water, extract with acetone:MeOH (1:1), followed by extraction with methylene chloride:2-propanol (75:25)	HPLC and GC/MS	50-1,100 ng/g	>90% recovery	Krahn and Malins 1982

TABLE 6-2 (Continued)

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Fish tissue (Cont.)	Homogenize fish tissue sample with distilled water and KOH pellets; reflux mixture and extract with methylene chloride; clean-up extraction basic alumina column	GC/MS	<0.2 ng/g	72% recovery	Vassilaros et al. 1982
	Homogenize fish sample in methylene chloride, shake and centrifuge; clean-up extract on alumina column	HPLC and GC/MS	No data	89%-98% recovery	Krahn et al. 1988
B(a)P Metabolite formulation	Dissolve sample in MeOH	HPLC/MS	ng/sample	No data	Bieri and Greaves 1987
PAH formulation	Dissolve PAH sample in methylene chloride	GC/MS with laser multiphoton ionization detection	200×10^{-15} g sample	No data	Rhodes et al. 1983
	Prepare solution of PAH sample in acetonitrile and analyze	UV-RRS	<1 ppb	No data	Asher 1984
	Prepere solution of PAH sample in ethanol	HPLC	500 to 16,000 ppb	No data	Su et al. 1982
	Insert PAH sample between glass-wool plugs in a glass tubing; convert PAH into nitroaromatic compound by passing N_2O_4 gas for 3 to 5 secs; analyze compound	TQMS	100 to 500 ppb	No data	Hunt et al. 1983

GC/MS = gas chromatography/mass spectrometry; TLC = thin-layer chromatography; GC/FID = gas chromatography/flame ionization detector; GC/DAD = gas chromatography/diode array detector; GC/LIMF = gas chromatography/laser induced molecular fluoresence; GC/ECD = gas chromatography/electron capture detector; GC/GPFD = gas chromatography/gas phase fluoresence detector; SP = spectrophotometer; RTP = room temperature phosphorescence; SLS = synchronous luminescence spectroscopy; GC/FT-IR = gas chromatography/fourier transform-infra-red spectrometry; HPLC = high performance liquid chromatography; HPTLC = high performance thin-layer chromatography; FSD = fluoresence scanning densitometry; XEOL = x-ray excited optical luminescence; SF = spectrofluorometer; FPS = fluoresence and phosphorescence spectrometry; LC = liquid chromatography; UV-RRS = ultraviolet-resonance raman spectrometer; RSD = relative standard deviation; DMSO = dimethyl sulfoxide.

Obana et al. (1981) reported the identification and quantification of six PAHs on EPA's priority pollutant list: anthracene, pyrene, benzo(b)-fluoranthene, benzo(k)fluoranthene, benzo(a)pyrene, and benzo(ghi)perylene using the HPLC/UV. Levels measured in human tissue ranged from 0.006 ng/g to 0.460 ng/g. The samples required extensive and rigorous cleanup procedures, including saponification and alumina and silica gel column chromatography, prior to analysis. The known carcinogens, benz(a)anthracene and dibenz(a,h)anthracene were not detected (detection limit less than 0.005 ng/g).

In addition to direct measurement of PAHs in biological tissues, it is also possible to determine the concentration of metabolites in biological fluids. Becher and Bjørseth (1983, 1985) and Becher (1986) developed an HPLC method for biological monitoring of PAHs and PAH metabolites in the urine of humans following occupational exposure to PAHs. Recoveries of the individual PAH compounds varied between 10% and 85% with the more volatile three-ring PAHs being the lowest. A detection limit of less than 1 μg of PAHs per mmol of creatinine was obtained. Hecht et al. (1979) employed HPLC analytical technique for determining the concentrations of benzo(a)pyrene and its metabolites in the feces of humans and rats following consumption of charcoal-broiled beef. A detection limit of 0.05 μg of benzo(a)pyrene metabolites per gram of sample was noted.

There is considerable evidence that PAHs are enzymatically converted to highly reactive metabolites that bind covalently to macromolecules such as DNA, thereby causing mutagenesis and carcinogenesis in experimental animals. Thus, benzo(a)pyrene, a prototype of the carcinogenic PAHs and the most thoroughly studied PAH, is activated by microsomal enzymes to 7_{β}, 8α-dihydroxy-$(9\alpha,10\alpha)$-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene (BPDE) and binds covalently to DNA, resulting in formation of the putative BPDE-DNA adducts (Harris et al. 1985; Haugen et al. 1986; Uziel et al. 1987). Sensitive methods are available to detect PAH-DNA adducts in the blood and tissues of humans and animals. These include ELISA, USERIA, ^{32}P-postlabeling, SLS, and HPLC.

ELISA technique is used for detection of antibodies in serum bound to BPDE-DNA adducts. The USERIA method involves measuring the immunological response of BPDE-DNA in the presence of rabbit anti-serum. Several researchers have employed the immunoassay techniques for detecting PAH-DNA adducts at 10^{-15} mol levels in the blood and tissues of humans occupationally exposed to PAHs (Amin et al. 1982; Harris et al. 1985; Haugen et al. 1986; Newman et al. 1988; Perera et al. 1988; Shamsuddin et al. 1985).

^{32}P-Postlabeling is a highly sensitive and specific method for detecting PAH-DNA adducts in blood and tissues of humans and animals (Philips et al. 1988, 1987; Weyand and Bevan 1987a). A detection limit of 0.3×10^{-15} mol of PAH adduct per μg of DNA (less than 1 adduct in 10^7 nucleotides) has been achieved (Phillips et al. 1988, 1987). A further advantage of ^{32}P-postlabeling technique is that adducts do not need to be fully characterized in order to be detected, and the method is particularly suited to occupational exposure of a complex mixture of PAHs.

Using benzo(a)pyrene as a model carcinogen, Vahakangas et al. (1985), Haugen et al. (1986), and Harris et al. (1985) have developed a SLS technique for detecting trace levels of PAH-DNA adducts in the blood of humans occupationally exposed to high levels of PAHs. Vahakangas and co-workers (1985) detected less than 1 benzo(a)pyrene moiety per 10^7 DNA by SLS technique following in vitro acid hydrolysis of BPDE-DNA adduct.

HPLC analytical method has been used for determining concentrations of PAH-DNA adduct and hydrolyzed PAH-DNA adducts in biological tissues and fluids (Autrup and Seremet 1986; Jongeneelen et al. 1986; Rice et al. 1985b; Salhab et al. 1987; Shugart 1986; Shugart et al. 1983; Weyand and Bevan 1987a). A detection limit of 10^{-15} mol of tetrols per sample was achieved (Haugen et al. 1986; Shugart et al. 1983; Weyand and Bevan 1987a).

6.2 ENVIRONMENTAL SAMPLES

The main difficulty associated with determination of PAHs in environmental samples is the extreme complexity of sample matrices. Even after extensive and rigorous cleanup, the PAH fraction may contain hundreds of compounds. Analytical methods that offer combinations of good chromatographic resolving power and detector selectivity are usually required to quantify selected compounds in such mixtures. There is essentially a three-step procedures for the analysis and determination of PAHs in environmental samples: (1) extraction and isolation of PAHs from the sample matrix; (2) column chromatographic separation (cleanup) of the PAH mixtures into subgroups or individual components; and (3) identification and quantitative determination of these subgroups or compounds.

A variety of analytical methods has been used for determining trace concentrations of PAHs in environmental samples. These include GC, HPLC, TLC, and others. Various detection devices used for GC quantification include flame ionization detector (FID), mass spectrometer (MS), fourier transformed infrared spectrometer (FT-IR), laser induced molecular fluorescence detector (LIMF), diode array detector (DAD), or gas phase fluorescence detector (GPFDA). GC/MS and HPLC are perhaps the most prevalent analytical methods for determining concentrations of PAHs in environmental samples.

Oehme (1983) and Low et al. (1986) employed capillary GC coupled to a negative ion chemical ionization MS for detecting and differentiating isomeric PAHs (including PAHs on EPA's priority pollutant list). This procedure was successfully used to differentiate the isomers benzo(j)fluoranthene and benzo(b)fluoranthene at low ppb levels in complex matrices, such as air particulate matter and coal fly ash. An alternative method for the elucidation of PAH isomers is GC coupled to a charge-exchange and chemical ionization MS (Simonsick and Hites 1985). Simonsick and Hites (1985) demonstrated that the structural isomers pyrene, fluoranthene, aceanthrylene and acephenanthrylene can be identified on the basis of their first ionization potential and $(M+1)^+/M^+$ mass ion ratio.

HPLC has been one of the most widely used analytical methods for determining PAHs in complex environmental samples. The development of a chemically nonpolar stationary phase for HPLC has provided a unique selectivity for separation of PAH isomers that are often difficult to separate by GC. For example, chrysene, benz(a)anthracene, and triphenylene are baseline resolved with a C-18 reverse phase column packing. A detection limit of subpicogram to picogram levels of PAHs per sample has been achieved by HPLC technique (Fox and Stanley 1976; Furuta and Otsuki 1983; Futoma et al. 1981; Golden and Sawicki 1978; Lawrence and Weber 1984; Marcomini et al. 1987; Nielsen 1979; Quilliam and Sim 1988; Risner 1988; Tomkins et al. 1982).

A number of new analytical techniques based on spectroscopic principles are being developed as possible alternatives to the chromatographic methods for determining PAHs. These include synchronous luminescence spectroscopy (SLS), room temperature phosphorescence (RTP), ultraviolet-resonance raman spectroscopy (UV-RRS), x-ray excited optical luminescence spectroscopy (XEOL), laser-induced molecular fluorescence (LIMF), and low-temperature fluorescence spectroscopy (LTFS) (Asher 1984; Garrigues and Ewald 1987; Lamotte et al. 1985; Popl et al. 1975; Richardson and Ando 1977; Vo-Dinh et al. 1984; Vo-Dinh 1981; Vo-Dinh and Abbot 1984; Woo et al. 1980).

SLS and RTP are the most widely used spectroscopic techniques for determining trace levels of PAHs in environmental media. Vo-Dinh (1981), Vo-Dinh and Abbot (1984), and Vo-Dinh et al. (1984) reported a cost-effective and relatively simple SLP and RTP technique for determining trace amounts of PAHs (less than 1×10^{-9} g per sample) in air particulate extracts collected at wood-burning area. Improved selectivity without loss of simplicity is the main advantage of SLS and RTP over conventional luminescence or fluorescence spectroscopy.

Methods 8100, 8250, and 8310 are the test methods recommended by EPA (1986) for determining PAHs at low μg per liter in water matrices. NIOSH (1985) has recommended methods 5506 and 5515 as the analytical methods for determining PAHs in air samples at below ppm level.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of PAHs is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of PAHs.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. A wide range of reliable analytical methods is available for detecting and quantifying PAHs and their metabolites in human tissues and body fluids. These analytical methods for measuring PAHs are sensitive enough to measure background levels in the population. Since the analytical methods are available to measure levels of PAHs at which presumably no health effects occur (i.e., background levels), levels of PAHs at which health effects occur should also be able to be detected. However, there is a need for analytical methods sensitive enough to detect and quantify, in human body fluids, all of the PAHs and their metabolites identified at NPL sites.

In addition to the analytical methods available for detecting and quantifying PAHs in human tissues and body fluids, sensitive methods are available to detect and quantitate benzo(a)pyrene-DNA adducts. The formation of the benzo(a)pyrene-DNA adduct may serve as a biomarker of PAH-induced carcinogenicity. These methods are useful for monitoring individuals occupationally or environmentally exposed to PAHs. Similar methods are currently not available for most of the other PAHs. Such methods, if available, would provide valuable information for determining short- and long-term effects of both carcinogenic and noncarcinogenic PAHs.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Standardized methods are available that are reliable and sensitive enough to detect PAHs in air, water, and soil. Exposure to PAHs is likely to occur near hazardous waste sites, which can contain concentrated sources of PAHs. Further research is needed to develop analytical methods that would simultaneously separate and quantify all or most of the PAHs found at NPL sites in highly complex (e.g., air and sediments) environmental matrices at ultra-trace (less than 1 ppt) levels. Such methods would permit researchers to assess the health effects of long-term exposure to PAHs and to delineate dose-response relationships.

6.3.2 On-going Studies

A. Weston, at the National Cancer Institute at the National Institutes of Health, is investigating the relationship between hydrocarbon-macromolecular adducts and human risk of developing cancer. This investigator proposes a model system using synthetically modified DNA to develop a more sensitive immunoassay system. Various immunological and physicochemical methods will be employed for the analysis of PAH-DNA adducts in human peripheral blood.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and advisories pertaining to PAHs in air, water, and food are summarized in Table 7-1.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Polycyclic Aromatic Hydrocarbons

Agency	Description	Value	References
IARC	Carcinogenic classification[a]		
	(B[b]F; B[k]f)	Group 2A	IARC 1973; IARC 1983
	(B[a]A; B[a]P; chrysene; DB[ah]A)	Group 2B	
	(Anthracene; fluoranthene; fluorene; I[123cd]P; phenanthrene; pyrene)	Group 3	
WHO	European Standard for Drinking Water[b]	0.2 μg/l	WHO 1977
	National		
Regulations:			
a. Air:			
OSHA	PEL (coal tar pitch volatiles - benzene soluble fraction[c])	0.2 mg/m^3	OSHA 1985 (29 CFR 1910.1002)
b. Non-specific media:			
EPA OERR	Reportable Quantity	1 lb	EPA 1987b (40 CFR 302)
Guidelines:			
a. Air:			
ACGIH	TLV TWA (coal tar pitch Volatiles - benzene soluble fraction[c])	0.2 mg/m^3	ACGIH 1986
NIOSH	REL TWA (benzene soluble PAHs)	0.1 mg/m^3	NIOSH 1985
	IDLH (coal tar pitch volatiles)	400 mg/m^3	
b. Water			
EPA OWRS	Ambient Water Quality Criteria for Protection of Human Health:		
	Ingesting water and organisms[d]		
	10^{-5}	28 ng/l	EPA 1980
	10^{-6}	2.8 ng/l	
	10^{-7}	0.28 ng/l	
	Organoleptic effects (acenaphthene)	0.02 mg/l	
	Fluoranthene	42 μg/l	EPA 1980
c. Non-specific media:			
EPA	Carcinogenic classification	Group B2[e]	EPA 1984
	State		
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations		NATICH 1988
Connecticut (B[a]P)		0.1000 μg/m^3 (8 hr avg)	
(coal tar pitch volatiles)		2.0000 μg/m^3 (8 hr avg)	
(fluorene)		50.000 μg/m^3 (8 hr avg)	
(naphthalene)		1000.0000 μg/m^3 (8 hr avg)	
Kansas (coal tar pitch volatiles)		0.0161 μg/m^3 (annual)	
Nevada (coal tar pitch volatiles)		0.0050 mg/^{3} (8 hr avg)	

TABLE 7-1 (Continued)

Agency	Description	Value	References
New York (B[a]P		0.0000	
North Carolina (coal tar pitch volatiles)		0.0000 mg/^{3} (24hr avg)	
Pennsylvania (Phila) (B[a]P)		0.0007 µg/m^3 (1 yr avg)	
(coal tar pitch volatiles)		0.4800 µg/m^3 (1 yr avg)	
Virginia (B[a]P)		0.0000 µg/m^3 (24 hr avg)	
(chrysene)		3.000 µg/m^3 (24 hr avg)	
(coal tar pitch volatiles)		2.0000 µg/m^3 (24 hr avg)	
b. Water:	Acceptable ambient water concentrations		
New York (sum of B[a]P, B[a]A, benzofluoranthenes, chrysene, fluoranthene, I[123cd]P, anthracene, pyrene, and MB[a]A)		0.2 µg/l	NYSDEC 1984
Kansas	Drinking water quality standards		FSTRAC 1988
(B[a]P)		0.03 µg/l	
(all other PAHs)		0.029 µg/l	
Maine		25 µg/l	
Minnesota		0.028 µg/l	
New Jersey (all PAHs)		1 µg/L	NJDEP 1989
New Mexico (B[a]P)		10 µg/l	
(all other PAHs)		30 µg/l	

[a] Group 2A = Probable human carcinogen; Group 2B = Possible human carcinogen; Group 3 = not classifiable as to carcinogenicity.

[b] The following PAHs were used as indicators in deriving this standard: B[a]P; B[b]F; B[a]F; B[k]F; fluoranthene; and I[123cd]P. Source: EPA 1986b.

[c] Includes anthracene, B[a]P, phenanthrene, acridine, chrysene and pyrene.

[d] Because of their carcinogenic potential, the EPA-recommended concentration for PAHs in ambient water is zero. However, because attainment of this level may not be possible, levels which correspond to upper bound incremental lifetime cancer risks of 10^{-5}, 10^{-6}, and 10^{-7} are estimated.

[e] Group B2 = Probable Human Carcinogen.

IARC = International Agency for Research on Cancer; B[b]F = benzo[b]fluoranthene; B[k]F = benzo[k]fluoranthene; B[a]A = benzo[a]anthracene; B[a]P = benzo[a]pyrene; DB[ab]A = dibenzo[a,b]anthracene; I[123cd]P = Indo-[1,2,3-cd]pyrene; WHO = World Health Organization; OSHA = Occupational Safety and Health Administration; PEL = Permissible Exposure Limit; EPA = Environmental Protection Agency; OWRS = Office of Water Regulations and Standards; TSCA = Toxic Substances Control Act; ACGIH = American Conference of Governmental Industrial Hygienists; TLV = Threshold Limit Value; TWA = Time-Weighted Average; NIOSH = National Institute for Occupational Safety and Health; REL = Recommended Exposure Limit; IDLH = Immediately Dangerous to Life and Health.

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the toxicological profiles.

Adsorption Coefficient (Koc) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

9. GLOSSARY

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

Lethal Concentration$_{(LO)}$ **(**LC_{LO}**)** -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ **(**LC_{50}**)** -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ **(**LD_{LO}**)** -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ **(**LD_{50}**)** -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ **(**LT_{50}**)** -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

9. GLOSSARY

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (Kow) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu g/L$ for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX

PEER REVIEW

A peer review panel was assembled for the PAHs. The panel consisted of the following members: Dr. Edmond J. LaVoie, Professor, Medicinal Chemistry, Rutgers University, College of Pharmacy; Dr. Joseph O'Connor, Research Associate Professor, Department of Environmental Medicine, New York University Medical Center; and Dr. Elaine Faustman, Assistant Professor, Department of Environmental Health, University of Washington. These experts collectively have knowledge of PAHs' physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in the Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

A joint panel of scientists from ATSDR and EPA has reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for these compounds. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility of the content of this profile lies with the Agency for Toxic Substances and Disease Registry.